Postmenopausal hormone therapy: risks and benefits

Serge Rozenberg, Jean Vandromme and Caroline Antoine

Abstract | Postmenopausal hormone therapy (PMHT) is used for the relief of menopausal symptoms, but the dosage has varied greatly throughout its existence. By the end of the 1990s, PMHT was mainly used to prevent chronic diseases such as osteoporosis, coronary heart disease and dementia, and large prevention trials were undertaken in this context. Following the initial negative reports of these trials, use of PMHT dramatically decreased. These reports noted surprisingly increased risks, notably of coronary heart disease, stroke and breast cancer, in people who used PMHT. Nowadays, considering the currently available data, it seems that an important distinction should be made between the treatment of climacteric symptoms in young, generally healthy, postmenopausal women and the prevention of chronic diseases in elderly women. PMHT seems to be beneficial and safe for postmenopausal symptomatic women aged <60 years. Treatments with a high safety profile should be the preferred option, including low-dose PMHT, oestrogen-only therapy in women who have had a hysterectomy, and vaginal oestrogen therapy for women with atrophic vaginitis. Nonandrogenic progestin might have a reduced thrombotic and breast cancer risk, and transdermal oestrogen could have a reduced thrombotic risk. Nevertheless, PMHT should not be used for the prevention of chronic diseases in the elderly (>70 years old) owing to the increased risk of stroke and breast cancer in these patients.

Rozenberg, S. *et al. Nat. Rev. Endocrinol.* **9**, 216–227 (2013); published online 19 February 2013; doi:10.1038/nrendo.2013.17

Introduction

The level of postmenopausal hormone therapy (PMHT) use has varied greatly throughout its 70 years of existence. Conjugated equine oestrogens were first marketed in 1942 for the treatment of women with menopausal symptoms. Sales initially soared rapidly, but fell dramatically in the late 1970s when the link between oestrogen use and endometrial cancer was clearly established.[1] In the 1980s, after the protective effects of progestins (compounds that interact with progesterone receptors in target tissues with effects similar to those of progesterone) on oestrogen-induced endometrial changes were established, PMHT use began to increase once again. Additionally, when PMHT was shown to have a preventive effect on loss of bone mass and on osteoporosis, use of this therapy increased further.[2–7] A maximum level of PMHT use was reached at the end of the 1990s at a time when animal studies, observational studies and randomized controlled trials all suggested that PMHT could prevent coronary heart disease and dementia.[8–11]

At the turn of the 21st century, approximately 15 million women in the USA were using PMHT.[12] The Heart and Estrogen/progenstin Replacement Study (HERS) and Women's Health Initiative (WHI) randomized controlled trials, in which the benefit of PMHT on chronic diseases was evaluated, were undertaken within the context of this level of PMHT use.[13,14] After the negative results of these two trials (showing that PMHT did not protect against heart disease and might even increase it) were reported in 2000 and 2002, respectively, PMHT use dramatically decreased.[15,16] These reports were followed by nearly 10 years of controversy regarding how to interpret the data.[17–20] In the past 5 years, after the reanalysis of the WHI trial data, many scientific societies have come to the conclusion that PMHT is beneficial for postmenopausal symptomatic women aged <60 years, but risks can be high in elderly women aged >70 years.[21–23]

In this Review, we have aimed to present a balanced view of the risks and benefits of PMHT and give advice for optimizing treatment in a variety of clinical situations. The general controversies in the field are touched upon and the advice presented is based on the best quality evidence available at the publication of the article.

What is in a name?

The controversy surrounding the treatment of oestrogen deficiency in women around the time of the menopausal transition is reflected in the terminology used to describe PMHT. Traditionally, the terms 'oestrogen replacement therapy' and 'hormone replacement therapy' have been used and are still the only 'mesh' terms that can be found in PubMed. However, other terms have emerged following publication of the WHI study results in 2002, such as 'menopausal hormone therapy' and PMHT. The term PMHT is broad and consists of many different regimens and compounds (Box 1).

Department of Obstetrics & Gynaecology, CHU Saint-Pierre, Université Libre de Buxelles, 322 rue Haute, 1000 Brussels, Belgium (**S. Rozenberg**, **J. Vandromme**, **C. Antoine**).

Correspondence to: S. Rozenberg serge_rozenberg@stpierre-bru.be

Competing interests
S. Rozenberg declares associations with the following companies/organizations: Abbot, Amgen, MSD, Pfizer, Will Pharma, Servier. See the article online for full details of the relationships. The other authors declare no competing interests.

Regimens, administration and doses

Oestradiol, oestradiol valerate and oestriol, which is a much weaker oestrogen, are often used in Europe, whereas conjugated equine oestrogens are the most widely used oestrogen-based PMHT in the USA and are the most studied. Paradoxically, preparations of conjugated equine oestrogens include a wide variety of oestrogenic compounds and might also contain compounds without oestrogenic activity.[24] Oestrogen-based PMHT is most often administered orally, but can also be given transdermally (as an implant) or vaginally.

A combination of oestrogenic and progestational compounds is generally included in PMHT. These forms of PMHT can differ in terms of their progestational, antioestrogenic, androgenic, antiandrogenic, antimineralocorticoid and glucocorticoid activities.[25] For instance, medroxy progesterone acetate, norethisterone acetate and levonorgestrel are commonly used in combination PMHTs and these progestational compounds have strong androgenic and glucocorticoid activities,[25] whereas other progestational compounds, such as didrogesterone, micronized progesterone and trimegestone, have less androgenic activity. Cyproterone acetate is known for its antiandrogenic effect, and drospirenone is known to have antimineralocorticoid activity.[25]

Oestrogen-based therapies can be used sequentially with a progestational compound. For example, oestrogen can be administered for a period of 20–28 days and the progestational compound is then added for a period of 10–14 days. Alternatively, oestrogen combined with progestational compounds can be taken continuously. PMHT can be administered orally or parenterally, as well as partially parenterally and partially orally. In Europe, a synthetic compound called tibolone, which has oestrogenic, progestogenic and androgenic actions, is often considered to be a PMHT. Bazedoxifene, a new selective oestrogen-receptor modulator can also be combined with conjugated equine oestrogen to form a tissue-selective oestrogen complex for delivery of PMHT (Box 1).[26]

The administered dose of oestrogen in PMHT preparations has been reduced steadily over the past 70 years to improve safety and reduce the incidence of adverse events. Daily doses of conjugated equine oestrogen as high as 2.5 mg and doses of 4 mg of oestradiol were used in the past; however, doses as low as 0.3 mg of conjugated equine oestrogen and 0.5 mg of oestradiol are now often used.

Indications for treatment

Climacteric symptoms

Results of systematic reviews and meta-analyses of randomized controlled trials have shown that systemic PMHT is the most effective treatment for the majority of menopausal symptoms, including hot flashes, sweating and joint pain. In women who have such symptoms, treatment with PMHT results in a 75% reduction in frequency and a 87% reduction in severity of the symptoms relative to treatment with a placebo.[27] Tibolone also alleviates postmenopausal symptoms, but to a slightly lesser extent.[28]

Key points

- Postmenopausal hormone therapy (PMHT) is indicated for the relief of menopausal symptoms in patients aged <60 years with climacteric symptoms
- Low doses of PMHT should be used when possible
- PMHT can be prescribed for a short period of time to treat osteoporosis when nonoestrogen therapies are unsuitable or in women who suffer simultaneously from climacteric symptoms and osteoporosis
- Use of a sequential progestin and a nonandrogenic progestin might be safer than use of continuous androgenic progestin
- Although data suggest that oestrogen therapy might prevent coronary heart disease, dementia and Alzheimer disease in young women, PMHT is not indicated for prevention of these conditions

Box 1 | Postmenopausal hormone treatment regimens

Oestrogen replacement therapy or oestrogen therapy

Includes an oestrogen only

Indicated in women who have had a hysterectomy or for vaginal therapy

Types: conjugated equine oestrogens, oestradiol, oestradiol valerate, ethinyl oestradiol, oestriol, ostradiol acetate, esterified oestrogen and oestropipate

Hormone replacement therapy or oestrogen and progesterone therapy

Includes an oestrogen and a progesterone

Sequential therapy

Oestrogen for 20–28 days followed by progesterone for 10–14 days

- Prescribed in late perimenopause or early postmenopause

Continuous therapy

- Prescribed in late menopause

Types

- Strong androgenic and/or glucocorticoid activity: medroxy progesterone acetate (oral), norethisterone acetate (orally or transdermal) or levonorgestrel (oral or intrauterine device)
- Low androgenic activity: didrogesterone (oral), micronized progesterone (oral or vaginal), trimegestone (oral) or norgestimate (oral)
- Antiandrogenic effect: cyproterone acetate (oral)
- Antimineralocorticoid activity: drospirenone (oral)

Tibolone

Has oestrogenic progestogenic and androgenic characteristics

Tissue-selective oestrogen complex

Conjugated equine oestrogen and bazedoxifene (a selective oestrogen-receptor modulator)

On the basis of data from randomized controlled trials, the effects of gabapentin, selective serotonin reuptake inhibitors and, to a lesser extent, the centrally acting α_2 adrenergic agonist clonidine might be useful for highly symptomatic women in whom use of PMHT is contraindicated, such as women with a history of breast cancer or thromboembolic disease. However, these drugs are not optimal choices for most women with postmenopausal symptoms. Other therapies, such as those that are based on *Actaea racemosa* (black cohosh), phytoestrogens or exercise intervention, have failed to reduce vasomotor symptoms in women experiencing postmenopausal symptoms when compared with placebo treatments.[29–36]

A clear dose–response effect exists with the use of PMHT in women with postmenopausal symptoms. Most early studies were conducted with daily doses containing the equivalent of 1 mg of oestradiol or 0.63 mg of conjugated equine oestrogen. However, low doses (0.5 mg of oestradiol and 0.3 mg of conjugated equine oestrogen)

Table 1 | Current major indications and contraindications for PMHT

Condition	Evidence and recommendation	Comments
Potential indications		
Moderate to severe climacteric symptoms	High-quality evidence, strong recommendation	Systematic PMHT Oestrogen therapy in case of hysterectomy
Vaginal atrophy	High-quality evidence, strong recommendation	Local oestrogen therapy
Osteoporosis	Moderate-quality evidence, weak recommendation	Systematic PMHT Treatment for a limited period of time, before shifting to other drugs when non-oestrogen therapies are unsuitable or when climacteric symptoms are also present
Overactive bladder	Moderate-quality evidence, weak recommendation	Local oestrogen therapy
Recurrent urinary tract infection	Moderate-quality evidence, weak recommendation	Local oestrogen therapy
Not indicated		
Genuine stress incontinence	High-quality evidence, weak recommendation	Condition might be worsened by systemic PMHT, and improved by vaginal oestrogen therapy
Prevention of coronary heart disease	High-quality evidence, weak recommendation	Oestrogen therapy might reduce the risk of atherosclerosis in young women early after menopause, but risk of coronary heart disease might be worsened as a result of thrombosis in at-risk patients
Colorectal cancer	High-quality evidence, weak recommendation	Some studies suggest a reduced risk among users of hormone replacement therapy
Prevention of dementia	Moderate-quality evidence, weak recommendation	Oestrogen therapy might decrease risk of cognition impairment in early menopause and oophorectomised patients, but PMHT might worsen dementia in elderly patients
Potential contraindicated		
Breast cancer survivors	Moderate-quality evidence, strong recommendation	Increased risk of recurrence
Endometrial cancer survivors	Low-quality evidence, weak recommendation	Few studies show no increase in recurrence of endometrial and ovarian cancer
Ovarian cancer survivors	Low-quality evidence, weak recommendation	Low-dose PMHT and transdermal therapy might be preferred in high-risk patients
Stroke	High-quality evidence, strong recommendation	NA
Thromboembolism	High-quality evidence, strong recommendation	The risk might not be increased using transdermal therapy

Abbreviations: NA, not available; PMHT, postmenopausal hormone therapy.

are sufficiently effective in most patients (~80%) and many physicians now suggest starting treatment with low doses (Table 1).[37]

Osteoporosis

In randomized controlled trials, hormone replacement therapy, oestrogen replacement therapy, tibolone therapy and use of a tissue-specific oestrogen complex have been consistently shown to prevent bone loss (as measured by dual-energy X-ray absorptiometry [DXA] or using bone turnover markers) even when low doses are used.[4,7,26,38–40] Similarly, in several randomized controlled trials and meta-analyses from the past decade, all types of PMHT have been reported to reduce the risk of fractures.[39,41] In both WHI trials, ~50 fractures per 10,000 person-years (~7 hip fractures and ~6 vertebral fractures) were prevented in women using PMHT.[41–43] Not surprisingly, this effect was only apparent for hip fractures in elderly women.[44–46] No proof of fracture reduction has been reported in randomized controlled trials including women using PMHT containing oestradiol doses ≤0.5 mg.

Since the 1990s, other antiosteoporosis drugs have been developed, including bisphosphonates, selective oestrogen-receptor modulators, synthetic parathyroid hormone, strontium ranelate and denosumab. These drugs are prescribed with calcium and vitamin D.[46]

PMHT is associated with an increased risk of breast cancer in women who receive this therapy long term, and with increased risk of stroke in elderly people (aged >70 years). Therefore, PMHT is not recommended solely for treating women with osteoporosis and, if it is used for this reason, PMHT should only be used for a short period of time, probably between 5 and 10 years, before other treatments are initiated. PMHT is also considered as a treatment for women who are at considerable risk of developing osteoporosis, but for whom non-oestrogen-based therapies are unsuitable. PMHT is also considered

for treating women who suffer simultaneously from osteoporosis and climacteric symptoms.[20,41,44,46] In guidelines published in 2012, the initiation of long-term oestrogen therapy to prevent osteoporosis is recommended in high-risk patients (Table 1).[22] These recommendations are based on the latest reports that have been published from the WHI trial in which oestrogen therapy was used. The latest findings show a greater benefit of this treatment for women with osteoporosis than previous findings.[21,47]

Urogenital atrophy and incontinence

About 70% of women with vaginal dryness and dyspareunia do not voluntarily mention this symptom to their general practitioner, even though they suffer from decreased quality of life as a result of these conditions.[48] Low oestrogen levels induce a reduction in the glycogen content of the vaginal epithelium, which leads to inhibition of lactic acid production in the vagina and an increase in vaginal pH.[48,49] Ultimately, these changes lead to an increased risk of vaginal atrophy, decreased vaginal blood flow, decreased lubrification, loss of elasticity and dyspareunia.[48,49] In women who only have symptoms as a result of vaginal atrophy, topical administration of oestrogen in the vagina is recommended and an added oral progestin is not necessary.[49] Alternative drugs are being developed to treat women with vaginal atrophy, including selective oestrogen-receptor modulators.[50]

Results of a meta-analysis showed that systemic administration of sequential oestrogen and progestin treatment or oestrogen therapy was associated with stress incontinence that was 10–30% worse in women receiving PMHT than in those receiving a placebo.[51] However, these results were heavily weighted by two trials in which the main end points measured were other conditions. Topical administration of oestrogens to the vagina was shown to improve incontinence by 25%.[51] In systematic reviews, oestrogen was shown to improve symptoms of overactive bladder and the frequency of recurrent urinary tract infection can be reduced using PMHT, and even more so using vaginal administration of oestrogen.[51]

Limited evidence exists that vaginal administration of oestrogen replacement therapy together with training of pelvic floor muscles is useful before surgery for pelvic organ prolapse.[52] However, oestrogen replacement therapy might facilitate surgery, by decreasing the atrophy of the vagina, and might reduce the risk of postoperative cystitis.

In clinical practice, incontinence should not be considered an indication for PMHT, whereas vaginal administration of oestrogen is indicated when patients have recurrent urinary tract infections, or dyspareunia owing to atrophic vaginitis or vaginal dryness (Table 1).[48,49,51]

Effects of PMHT on chronic diseases

Cardiovascular diseases

Coronary heart disease

The influence of PMHT on cardiovascular disease, particularly on coronary heart disease (CHD), is one of the most controversial subjects of the past decade. Previously, results of studies in animals, observational studies and randomized controlled trials in which surrogate end points were measured, such as biological markers (levels of lipids and C-reactive protein), or radiological markers (coronary atherosclerosis progression), showed that PMHT had both primary and secondary protective effects on CHD.[8,10,53–55] In the wake of these studies, randomized controlled trials were designed to investigate the possibility of using PMHT to prevent cardiovascular disease.[13,14]

The results of the HERS trial, in which women with CHD were given either PMHT (consisting of a combined equine oestrogen and medroxy progesterone acetate) or a placebo, showed no favourable results on secondary prevention of CHD.[15] Even more startlingly, the initial results of the WHI trial, in which the same form of PMHT was used, showed that PMHT increased the risk of developing CHD.[16] Following these reports, regulatory authorities, including the FDA and the European Medical Agency, recommended that the use of PMHT should be restricted to treating women with postmenopausal symptoms, and that such therapy should only be used for short periods of time. In 2012, results of a meta-analysis showed that combined continuous therapy with oestrogen and progesterone significantly increased the risk of experiencing a coronary event by two cases per 1,000 patients after 1 year of use (95% CI 3–7).[56] However, most of the data were derived from women aged >60 years who had some degree of comorbidity.[56] By contrast, in reports from the WHI trial in which conjugated equine oestrogen alone was used, no modification of the CHD risk was reported.[43] Additionally, in the 10-year follow-up period after the WHI study, women aged 50–59 years who received conjugated equine oestrogen treatment experienced 12 fewer acute myocardial infarctions per 10,000 person-years than those receiving a placebo. However, among women aged 70–79 years, those receiving the PMHT experienced 16 more myocardial infarctions per 10,000 person-years than those receiving the placebo.[21]

Coronary plaque accumulation is reduced by half among young women treated with oestrogen, particularly among those who were adherent to their treatment, but not among elderly women.[57–59] Consequently, oestrogen might have beneficial effects on the development of atherosclerosis, but only when it is prescribed soon after the onset of menopause—in young, healthy patients. However, in old, unhealthy patients, the risk of thrombosis outweighs the benefit of atherosclerosis inhibition. These results suggest the existence of a theoretical window of opportunity for using PMHT to reduce the risk of developing CHD.[20,22,55,60–65] Some researchers have observed an association between the severity of hot flashes and a vasodilatory effect during endothelial function testing. These observations suggest that vascular function and the activity of the sympathetic nervous system is altered in severely symptomatic postmenopausal patients.[63] Such findings suggest that PMHT might have a protective effect on CHD in symptomatic women but not in asymptomatic women.

In a cohort of 1,006 healthy women aged 45–58 years, those who had been randomly assigned to receive PMHT in an open-label study had a 50% lower risk of mortality, heart failure and myocardial infarction after 10 years of treatment than did women who received no therapy.[64] Moreover, adding medroxy progesterone acetate to oestrogen replacement therapy might have an unfavourable effect on CHD risk.[10] However, addition of other progestins, such as micronized progesterone or didrogesterone, might not diminish the beneficial effects caused by 17β-oestradiol as much as medroxy progesterone acetate.[20]

In clinical practice, PMHT is not currently recommended for primary or secondary prevention of CHD in postmenopausal women (Table 1). Women with cardiovascular risk factors who are seeking PMHT because of troublesome climacteric symptoms should be evaluated for their individual baseline risk of cardiovascular disease (Supplementary Table 1 online). Risks should be weighed against expected benefits from symptomatic relief and improved quality of life.

Stroke

In most systematic reviews and meta-analyses in the field over the past two decades, researchers have reported that oestrogen replacement therapy, therapy with oestrogen and a progesterone, and treatment with tibolone are associated with an increased risk of experiencing ischaemic stroke (~30%).[28,40,65–67] Age does not modify the magnitude of the relative risk, but influences those of the absolute and attributed risks. The risk of experiencing ischaemic stroke might also be dose dependent: a reduced risk has been reported in patients using low doses of oral oestrogen-only therapy or combined oestrogen and progesterone therapy.[68] However, in other studies, a reduced risk has only been observed when patients were using transdermal oestrogen therapy.[69,70]

As the basal risk of experiencing stroke increases exponentially with age, PMHT might be responsible for less than one additional case of stroke per 10,000 women per year who are receiving this therapy before the age of 50, and 1.5 cases for women aged 50–55 years, two cases for women aged 55–60 years, three cases for women aged 60–65 years and seven cases in women aged >65 years.[68] This potential risk should not prevent young women with postmenopausal symptoms from using PMHT. However, in older women (that is, those aged >65 years), the risk of stroke that is associated with PMHT could outweigh the benefits of using it. On the basis of the available data, low dose, transdermal therapy might be the preferred PMHT in patients at high risk of experiencing ischaemic stroke (Supplementary Table 1 online).[68–70]

Thromboembolic disease

Results of meta-analyses have consistently shown that oral oestrogen therapy doubles or triples the risk of a woman experiencing venous thromboembolism.[56,67] Combined therapy with oestrogen and progesterone increases the risk of experiencing venous thromboembolism relative to oestrogen monotherapy.[67] Current data suggest that the risk of venous thromboembolism is not increased in women who are using transdermal oestrogen therapy.[69–72]

PMHT increases the risk of experiencing venous thromboembolism, particularly during the first year of treatment. Therefore, women should be assessed for the presence of risk factors for venous thromboembolism before PMHT is initiated.[73] Transdermal oestrogen treatment might be safer than other forms of PMHT with respect to thrombotic risk. Observational studies suggest that micronized progesterone or dydrogesterone have a better risk profile than other progestins with regard to thrombotic risk (Table 1).[69–73]

Cancer

Breast cancer

The increased risk of developing breast cancer that is associated with use of PMHT might be dependent on the population of patients, regimen type and dose administered. An increased risk of breast cancer has been found in women who have received ≥5 years of continuous treatment with oestrogen and progestin.[74] The increased risk of developing breast cancer in women receiving PMHT might also be associated with increased mortality.[23,74,75]

The increased risk of breast cancer in women receiving long-term continuous therapy with oestrogen and progestin is illustrated in results of analyses of data collected from women regarding use of such therapy before entering the WHI study. Women who received therapy with oestrogen and progestin had a significantly increased risk of breast cancer, but no such increased risk existed in women who had not previously been treated with PMHT. However, risk of breast cancer did increase slightly with increasing duration of PMHT in women who had not previously used PMHT and in women who were very adherent to oestrogen and progestin therapy.[74]

In the latest published report of the WHI trial follow-up period, a decrease in the incidence of breast cancer was found in women who had received therapy with oestrogen alone compared with women who had received a placebo.[21] Similarly, the LIFT trial investigators also reported a lower risk of breast cancer in women who received tibolone than in women who were given a placebo.[40] In the initial report of the French observational E3N study, no increase in the risk of breast cancer was noted in women who received therapy with oestrogen alone, or in women who received combined therapy consisting of oestrogens with micronized progesterone or dydrogesterone.[76] However, in this trial, an increased risk of developing breast cancer was observed in women who were using combined therapy consisting of oestrogen and so-called androgenic progestins, which include medroxyprogesterone acetate and norethisterone acetate.[76] In the latest report from the E3N study, increased risk of breast cancer was reported to occur in women after long-term use of PMHT. However, this increase in risk was less in women who were receiving oestrogen-only therapy or therapy with combined oestrogen and micronized progesterone or dydrogesterone than in women who were receiving oestrogen combined

with androgenic progestins.[76] Sequential use of the progestin norethisterone acetate seems to be less associated with increased risk of breast cancer than continuous use of progestin.[77] The risk of developing breast cancer has been suggested to be higher if combined oestrogen and progesterone therapy that contains androgenic progestins is started soon after the onset of menopause.[76,78–80] This association is more evident in slim women (BMI <25),[80] women with baseline breast tenderness[81] and women with high baseline breast density, as determined using mammography.[82] The risk of developing breast cancer in women who received PMHT decreases within 2 years of hormone therapy being stopped, which suggests a regression of preclinical cancers.[80,83]

On the basis of the WHI data, 5 years of PMHT use in women aged 50–60 years would be responsible for five additional cases of breast cancer per 10,000 women every year.[44] Therefore, individualized baseline risk should be evaluated before PMHT is considered (Supplementary Table 1 online). Medical practitioners should be cautious when initiating combined oestrogen–progesterone therapy too soon after the onset of menopause and when PMHT is initiated, low doses should be favoured.[76,78,80]

Endometrial cancer

The baseline incidence of endometrial cancer has increased in the past two decades in line with the increase in prevalence of risk factors for this cancer, such as obesity and type 2 diabetes mellitus. Administration of PMHT consisting of oestrogen alone after menopause increases the risk of developing endometrial hyperplasia and endometrial cancer.[84] This increase in risk is dependent on the dose given and the duration of treatment. The magnitude of the increase varies from a twofold to a 10-fold increase in risk.[84] However, use of combination oestrogen and progesterone treatment decreases the risk of developing endometrial hyperplasia and endometrial cancer, provided that the progestin is prescribed for a sufficient number of days, for example, 10–12 days per month.[85,86] Similarly, the risk of developing endometrial cancer was not increased in the WHI trial in which women received treatment with combined oestrogen and progesterone.[41,87]

In clinical practice, the most commonly used regimen for women receiving PMHT during or soon after the menopausal transition is sequential treatment with an oestrogen and a progestin for ≥12 days per month.[86] In postmenopausal women who want to avoid vaginal bleeding, the most common regimen that is prescribed is continuous combined oestrogen and progesterone (Box 1). Continuous combined regimens provide higher protection from endometrial cancer than do sequential regimens. In women who have undergone hysterectomy, addition of a progestin to their PMHT regimen is not necessary. Treatment with progestins is considered to be unnecessary in women who are using vaginal oestriol therapy or small doses of vaginal oestradiol.

Ovarian cancer

No significant difference in the risk of ovarian cancer was noted in reports from the WHI study.[87] However, results of a systematic review of mainly observational studies showed that therapy with oestrogen alone and with oestrogen and progesterone might be associated with an increased risk of developing ovarian cancer.[88] Similarly, in a separate study, associations between ovarian cancer and both oestrogen replacement therapy (a 20% increase) and therapy with oestrogen and progesterone (a 10% increase) have been observed.[89] Whether this risk is also observed when progestins are administered daily is not clear. One observational study demonstrated an increased risk of both serous tumours and endometrioid tumours, but a decreased risk of mucinous tumours in women using oestrogen replacement therapy or combined therapy with oestrogen and progesterone.[90]

The lifetime risk of postmenopausal women developing ovarian cancer is low (1.4% for women aged 50 years in the USA).[91] In the WHI trial, the rate of diagnosis of ovarian cancer was 42 per 100,000 person-years in women using combined therapy with oestrogen and progesterone and 27 per 100,000 person-years in women using a placebo.[87] The attributable risk would, therefore, be in the range of one case per 10,000 person-years. Furthermore, this risk is age-related; women aged >60 years are more likely than younger women to develop ovarian cancer. In addition, the risk is probably related to long-term oestrogen replacement therapy rather than to other types of PMHT. Nevertheless, ovarian cancer has a poor prognosis, so it might be prudent for the patient's risk of ovarian cancer to be considered if the woman has not undergone prophylactic oophorectomy.

Colorectal cancer

A reduced risk of colorectal cancer among users of hormone replacement therapy has been found in several meta-analyses.[41,92] Similarly, in the WHI trial in which combined oestrogen and progesterone treatment was used, a 46% reduced rate of colorectal cancer was observed among women who received PMHT in comparison with those who received a placebo. However, paradoxically, the cancer stage was slightly more advanced at the time of diagnosis among users of hormone replacement therapy who developed colorectal cancer.[93] No difference in prevalence of colorectal cancer, or in the prognosis of women who developed the disease, was observed in the WHI trial in which women received oestrogen alone.[21] Various hypotheses have been put forward to explain the apparently contradictory results among studies. One theory is that oestrogen has a role in reducing concentrations of bile acid in the colon and another is that progestins have antiproliferative effects.

In clinical practice, initiating PMHT should not be considered a prevention strategy for colorectal cancer. Conversely, women at high risk of developing colorectal cancer should not be excluded from receiving PMHT when they are symptomatic.

Lung cancer

Little data exist regarding the incidence of or mortality associated with pulmonary cancer in relation to PMHT use. No increased incidence was found in the WHI trials

in which oestrogen alone or combined oestrogen and progesterone therapy was used.[94,95] In *post hoc* analyses, however, increased mortality as a result of lung cancer, mainly from non-small-cell lung cancers, was found,[95] but this result was based on a small series of patients.[95]

In clinical practice, the effect of PMHT on lung cancer is probably not clinically relevant for most patients. Attention should instead be focused on the effect of other risk factors such as smoking.

Effects of PMHT on survivors of cancer

Survivors of breast cancer

Most published reports in this area are not based on clinical trials, and are subject to multiple biases.[96] Results of a few clinical trials involving women who have survived breast cancer have been published, but are inconsistent in terms of safety data.[97–100] In both the LIBERATE trial[100] (tibolone versus placebo) and the HABITS trial[99] (PMHT versus no treatment) an increased rate of recurrence of breast cancer was observed. However, this increase was not seen in women treated with PMHT who were enrolled in the Stockholm trial, the results of which have been updated in 2012 to provide data on the 10-year follow-up period.[101]

The differences in the results of HABITS and Stockholm trials could be because of heterogeneity in the groups of patients studied. For example, the patients in the HABITS trial had a higher number of involved nodes, a lower frequency of tamoxifen treatment, and a higher frequency of combined oestrogen and progestin therapy use than patients in the Stockholm trial.[96–98] Nevertheless, a combined analysis of the HABITS and Stockholm trial data also found an increased risk of breast cancer recurrence.[96] In the LIBERATE trial, the increased risk of metastases occurring in the patients receiving concomitant treatment with aromatase inhibitors was of particular concern.[100]

Whether vaginal oestrogen therapy should be used in women who have atrophic vaginitis that severely affects their sexual activity has also been debated.[102] While concerns exist, many clinicians advise their patients to try nonhormonal therapy, such as moisteners and lubrication, and prescribe a weak oestrogenic compound, such as oestriol, only if alternatives have failed to achieve sufficient results.[103,104] Most guidelines recommend that survivors of breast cancer should not be treated with conventional PMHT, and that other strategies should be tried first.[104,105]

Survivors of endometrial cancer

Few studies have shown that recurrence rates of endometrial cancer are unaffected among survivors of endometrial cancer who use oestrogen therapy.[106–108] However, reports of surveys note that many gynaecologists are still likely to prescribe oestrogen therapy to women with postmenopausal symptoms even if they have a history of early-stage endometrial cancer.[109] Results of at least one study suggest that recurrence of endometrial cancer is more frequent among black women who use oestrogen therapy than among white women receiving similar treatment.[110] A variation in the metabolism of oestrogen might explain the higher recurrence rate observed in black women than in white women.[110] As a result of limitations in the existing studies, sufficient data is lacking to support the safety of PMHT in endometrial cancer survivors.[111] Alternative nonhormonal treatments are therefore often tried first.

Survivors of ovarian cancer

Whether PMHT with oestrogen alone modifies survival and recurrence rates of ovarian cancer in patients receiving this type of PMHT has only been evaluated in a few studies that were likely to have been underpowered.[111] In a study involving 130 women aged <60 years, therapy with oestrogen alone did not have a negative influence on the disease-free interval or overall survival in those who had a history of ovarian carcinoma.[112] As a result of the limitations of studies, many physicians prefer to withhold oestrogen therapy in such patients and instead prescribe alternative nonhormonal treatments. Conversely, others feel that it is not necessary to withhold oestrogen replacement therapy from any symptomatic woman with ovarian malignancy regardless of their risk category.[113]

Effect of PMHT on cognition and dementia

Results of experiments in cellular models and animals, as well as neuroimaging and observational studies, have suggested a neuroprotective role of oestrogen therapy that is initiated soon after the onset of menopause.[11,114–119] However, the evidence of a beneficial effect in women receiving PMHT remains sparse. Indeed, in the WHI trial, women aged 65–79 years who received therapy with oestrogen and progesterone had about 22 more events of probable dementia per 10,000 person-years than women who received a placebo.[41,119] This increase was not seen in women in the WHI trial in which oestrogen monotherapy was used. Oestrogen might have different effects on the brain depending on the age of the patient, age at time of PMHT initiation, type of menopause (natural versus medically or surgically induced) and type of PMHT used.[11,41,115–119]

The conflicts in the data might be explained by the 'window of opportunity hypothesis' described above. For example, whereas oestrogen treatment might have a neuroprotective effect in women who have undergone bilateral oophorectomy before the onset of menopause, in women who experienced premature or early natural menopause, or in women who start PMHT soon after the onset of the menopause, PMHT might have deleterious effects on cognitive function in elderly patients or in those who start PMHT several years after the onset of menopause,[44,114–119] The deleterious effects might be attributable to the increased risk of thrombosis in these women.[65]

PMHT is not indicated for primary or secondary prevention of dementia, or for preventing the deterioration of cognitive function in postmenopausal women.[56] However, PMHT in women who are young when they enter menopause or undergo oophorectomy might have a favourable effect on cognition.

Effect of PMHT on quality of life

Evaluation of the long-term effect of PMHT on quality of life is difficult. Women who participate in long-term randomized controlled trials are mostly asymptomatic and in such women, PMHT has only been shown to modestly improve sleeping and sexual satisfaction without improving general quality of life.[120] In asymptomatic women, PMHT might even worsen quality of life, owing to the presence of adverse effects such as vaginal bleeding.[48,56,121] However, when climacteric symptoms are experienced frequently or are severe, PMHT can dramatically and rapidly improve quality of life.[44,122] Therefore, only women experiencing postmenopausal symptoms should be advised to use PMHT with the goal of improving quality of life.

Global effect of PMHT on mortality

Long-term mortality data have been generated in only a few randomized controlled trials.[21,43,56,64,75,123] In the two WHI trials, no difference in mortality was observed.[47,123] Results of *post hoc* analyses, however, showed that 13 fewer deaths per 10,000 women were observed over the average follow-up period of 10.7 years in those aged 50–59 years who received conjugated equine oestrogen therapy than in those who received placebo.[21] By contrast, 19 more deaths occurred in women aged 70–79 years who received conjugated equine oestrogen therapy than in women who received a placebo.[21,47] The results of these *post hoc* analyses are reassuring, as PMHT is mostly prescribed to young women at the beginning of the menopausal transition. Similarly, women aged 50 years who were treated with PMHT had a mortality that was half of that in untreated control women.[64]

Observational studies that were undertaken before the WHI trial showed that use of an oestrogen and progesterone was associated with reduced mortality, probably owing to a decrease in cardiovascular-disease-related deaths. However, this finding could have been as a result of a healthy user bias.[124,125] Reports of studies in the past decade have also suggested that the association between PMHT use and mortality could vary depending on genetic profile and, more specifically, ESR1 and ESR2 polymorphisms.[126] Currently, PMHT should not be initiated for long-term reduction of mortality in older women (aged >60 years). Conversely, in younger women (aged around 50 years), PMHT could possibly reduce mortality.[68,127]

PMHT for preventing chronic diseases

On the basis of a report of follow-up data from the WHI trial,[51] the US Preventive Services Task Force recommends that PMHT should not be used for the sole purpose of preventing chronic diseases.[127] Importantly, these recommendations do not apply to women who are considering using PMHT for the management of menopausal symptoms, such as hot flashes or vaginal dryness, or to women aged <50 years in whom menopause is surgically induced.[127]

PMHT in atypical clinical situations

Premature menopause

Data from studies in which elderly women were included are probably not representative of women who suffer from premature menopause (that is, menopause that begins in women aged <40 years), or even from early menopause (before age 45). For example, results of observational studies have shown that bilateral oophorectomy at a young age (<45 years) is associated with increased mortality and increased risk of developing cardiovascular disease, neurological disorders (such as dementia or Parkinson disease) and osteoporosis, and even more so, when these women are not treated with PMHT.[128,129] Therefore, although no strong data exist regarding the risk:benefit ratio of PMHT use in young women, use of PMHT is generally advised for women who have undergone premature menopause until they are aged 50 years.[12,22,44]

Young patients with oestrogen deficiency

Oestrogen deficiency can occur as a result of a congenital anomaly (such as Turner syndrome) but can also be acquired because of functional hypothalamic amenorrhea. The latter cause is often attributable to eating disorders (such as anorexia nervosa), exercise or stress. Weak evidence exists that oestrogen treatment has a moderate effect on improving lumbar spine BMD (but not femoral-neck BMD) in young patients with anorexia nervosa.[130] Oestrogen therapy is unnecessary for such patients when weight gain is achieved and menses resume. However, patients who do not meet their weight-gain goal and/or in whom menses does not resume are often prescribed supplements such as calcium and vitamin D, and oestrogen preparations.

Individualization of risk assessment

Many menopause and endocrine societies agree that PMHT use needs to be individualized and that prescription should be based on an evaluation of the risk:benefit ratio.[20,22,23] A patient's baseline risk of developing important diseases that have been associated with PMHT use, such as osteoporosis and breast cancer, can be estimated through systematic assessment of risk factors. Additionally, tools have been developed for assessing risk of developing specific conditions (Supplementary Table 1 online).[131–138] The clinician should be aware that all of the available tools have limitations and might not apply to all patients. Furthermore, few of these tools include use of PMHT when calculating their assessment of risk.

Future areas of research

The past decade has provided a large amount of data regarding the use of PMHT. They underline that not all women who use PMHT are exposed to the same risks, and that not all PMHTs have similar risk profiles. Current research is focused towards developing safe regimens. Treatment with oestrogen alone seems to be safer than combined treatment with oestrogen and progesterone, and some nonandrogenic progestins seem to be safer than androgenic progestins. New drugs that could be used include oestetrol and new members of the selective-oestrogen-receptor-modulator class. The selective oestrogen-receptor modulators could be used alone or combined with oestrogen therapies, such as

tissue-selective oestrogen complexes. Novel regimens could reduce the current risks of using oestrogen and progesterone therapies, particularly with regards to risk of breast cancer.

Various hypotheses will be tested in the coming years to determine why effects differ between treatments. Future studies should improve understanding of how the different compounds interact with signalling pathways and influence gene transcription.[139,140] As genetic susceptibility to risks associated with use of PMHT might also exist, genetic testing could be used in the future to determine who will or will not benefit from PMHT.[141] Use of lifestyle and alternative treatment strategies that could alleviate postmenopausal symptoms might also be investigated.

Conclusions

As most women considered for PMHT are aged <60 years and healthy, their baseline risk for most pathologies is low and only slightly modified by PMHT use.[20] These women need to be reassured that if the treatment is indicated, it can be prescribed safely, but their need for PMHT should be reassessed regularly. In many cases, the treatment can be tapered down or stopped after a few years of use.

In elderly women with postmenopausal symptoms or in women with prevalent risk factors for stroke, thrombosis and breast cancer, the expected benefits of PMHT need to be weighed against these risk factors. Transdermal oestrogen therapy or low-dose oestrogen therapy could be used as these therapies are associated with lower thrombotic risk than conventional oral oestrogen therapies. Alternative therapies, such as nonhormonal treatments, can be tried first. For patients with atrophic vaginitis, vaginal oestrogen is generally required for extended periods of time. PMHT can be prescribed for osteoporosis for a short period of time, before shifting to other drugs, or for women for whom non-oestrogen therapies are unsuitable or for women who suffer simultaneously from climacteric symptoms. PMHT is not indicated for CVD prevention, dementia or incontinence. PMHT is generally contraindicated for women with a previous history of breast cancer, stroke and thromboembolic disease.

Review criteria

For this Review, MEDLINE searches were performed using different combinations of the following terms: "hormone replacement therapy" or "estrogen replacement therapy," and "hot flashes, urinary incontinence, vaginal atrophy, osteoporosis, breast-, endometrium, ovarian, colorectal, lung cancer, coronary heart disease, stroke, thromboembolism, dementia, mortality, quality of life". Literature considered were systematic reviews, meta-analyses, large randomized controlled trials in which event outcomes were assessed, and large observational studies in which the effect of hormone replacement therapy and oestrogen replacement therapy were assessed. For most clinical issues, papers published between 2000 and September 2012 were considered. Other databases (including the Cochrane Database of Systematic Reviews) were also searched. Whenever possible, reports in which results were expressed in terms of absolute risk and attributed risk were used rather than those in which a relative risk, hazard ratio or odds ratio were given.

1. Smith, D. C., Prentice, R., Thompson, D. J. & Herrmann, W. L. Association of exogenous estrogen and endometrial carcinoma. *N. Engl. J. Med.* **293**, 1164–1167 (1975).
2. Hammond, C. B., Jelovsek, F. R., Lee, K. L., Creasman, W. T. & Parker, R. T. Effects of long-term estrogen replacement therapy. II. Neoplasia. *Am. J. Obstet. Gynecol.* **133**, 537–547 (1979).
3. Lindsay, R., Hart, D. M., Forrest, C. & Baird, C. Prevention of spinal osteoporosis in oophorectomised women. *Lancet* **2**, 1151–1154 (1980).
4. Rozenberg, S., Vandromme, J., Kroll, M., Pastijn, A. & Degueldre, M. Osteoporosis prevention with sex hormone replacement therapy. *Int. J. Fertil. Menopausal Stud.* **39**, 262–271 (1994).
5. Udoff, L., Langenberg, P. & Adashi, E. Y. Combined continuous hormone replacement therapy: a critical review. *Obstet. Gynecol.* **86**, 306–316 (1995).
6. Pickar, J. H., Thorneycroft, I. & Whitehead, M. Effects of hormone replacement therapy on the endometrium and lipid parameters: a review of randomized clinical trials, 1985 to 1995. *Am. J. Obstet. Gynecol.* **178**, 1087–1099 (1998).
7. Dören, M., Nilsson, J. A. & Johnell, O. Effects of specific post-menopausal hormone therapies on bone mineral density in post-menopausal women: a meta-analysis. *Hum. Reprod.* **18**, 1737–1746 (2003).
8. Barrett-Connor, E. *et al.* The Postmenopausal Estrogen/Progestin Interventions Study: primary outcomes in adherent women. *Maturitas* **27**, 261–274 (1997).
9. Grodstein, F. *et al.* A prospective, observational study of postmenopausal hormone therapy and primary prevention of cardiovascular disease. *Ann. Intern. Med.* **133**, 933–941 (2000).
10. Clarkson, T. B. & Appt, S. E. Controversies about HRT—lessons from monkey models. *Maturitas* **51**, 64–74 (2005).
11. Sherwin, B. B. & Henry, J. F. Brain aging modulates the neuroprotective effects of estrogen on selective aspects of cognition in women: a critical review. *Front. Neuroendocrinol.* **29**, 88–113 (2008).
12. Stefanick, M. L. Estrogens and progestins: background and history, trends in use, and guidelines and regimens approved by the US Food and Drug Administration. *Am. J. Med.* **118** (Suppl. 12B), 64–73 (2005).
13. Hulley, S. *et al.* Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group. *JAMA* **280**, 605–613 (1998).
14. Rossouw, J. E. Estrogens for prevention of coronary heart disease. Putting the brakes on the bandwagon. *Circulation* **94**, 2982–2985 (1996).
15. Hulley, S. Estrogens should not be initiated for the secondary prevention of coronary artery disease: a debate. *Can. J. Cardiol.* **16** (Suppl. E), 10E–12E (2000).
16. Manson, J. E. *et al.* Estrogen plus progestin and the risk of coronary heart disease. *N. Engl. J. Med.* **349**, 523–534 (2003).
17. Solomon, C. G. & Dluhy, R. G. Rethinking postmenopausal hormone therapy. *N. Engl. J. Med.* **348**, 579–580 (2003).
18. Ena, G. & Rozenberg, S. Issues to debate on the Women's Health Initiative (WHI) study. Prescription attitudes among Belgian gynaecologists after premature discontinuation of the WHI study. *Hum. Reprod.* **18**, 2245–2248 (2003).
19. Bush, T. M. *et al.* How the Women's Health Initiative (WHI) influenced physicians' practice and attitudes. *J. Gen. Intern. Med.* **22**, 1311–1316 (2007).
20. Gompel, A., Rozenberg, S., Barlow D. H. & EMAS board members. The EMAS 2008 update on clinical recommendations on postmenopausal hormone replacement therapy. *Maturitas* **61**, 227–232 (2008).
21. LaCroix, A. Z. *et al.* Health outcomes after stopping conjugated equine estrogens among postmenopausal women with prior hysterectomy: a randomized controlled trial. *JAMA* **305**, 1305–1314 (2011).
22. North American Menopause Society. The 2012 hormone therapy position statement of: The North American Menopause Society. *Menopause* **19**, 257–271 (2012).
23. Stuenkel, C. A. *et al.* A decade after the Women's Health Initiative—the experts do agree. *J. Clin. Endocrinol. Metab.* **97**, 2617–2618 (2012).
24. Notelovitz, M. Clinical opinion: the biologic and pharmacologic principles of estrogen therapy for symptomatic menopause. *MedGenMed.* **8**, 85 (2006).

25. Nath, A. & Sitruk-Ware, R. Different cardiovascular effects of progestins according to structure and activity. *Climacteric* **12** (Suppl. 1), 96–101 (2009).
26. Palacios, S. *et al.* EMAS clinical guide: selective estrogen receptor modulators for postmenopausal osteoporosis. *Maturitas* **71**, 194–198 (2012).
27. Maclennan, A. H., Broadbent, J. L., Lester, S. & Moore, V. Oral oestrogen and combined oestrogen/progestogen therapy versus placebo for hot flushes. *Cochrane Database of Systematic Reviews*, Issue 4. Art. No.: CD002978. http://dx.doi.org/10.1002/14651858.CD002978.pub2.
28. Formoso, G. *et al.* Short and long term effects of tibolone in postmenopausal women. *Cochrane Database of Systematic Reviews*, Issue 2. Art. No.: CD008536. http://dx.doi.org/10.1002/14651858.CD008536.pub2.
29. Nelson, H. D. *et al.* Nonhormonal therapies for menopausal hot flashes: systematic review and meta-analysis. *JAMA* **295**, 2057–2071 (2006).
30. Antoine, C., Liebens, F., Carly, B., Pastijn, A. & Rozenberg, S. Safety of alternative treatments for menopausal symptoms after breast cancer: a qualitative systematic review. *Climacteric* **10**, 23–26 (2007).
31. Loprinzi, C. L. *et al.* Newer antidepressants and gabapentin for hot flashes: an individual patient pooled analysis. *J. Clin. Oncol.* **27**, 2831–2837 (2009).
32. Toulis, K. A., Tzellos, T., Kouvelas, D. & Goulis, D. G. Gabapentin for the treatment of hot flashes in women with natural or tamoxifen-induced menopause: a systematic review and meta-analysis. *Clin. Ther.* **31**, 221–235 (2009).
33. Rada, G. *et al.* Non-hormonal interventions for hot flushes in women with a history of breast cancer. *Cochrane Database of Systematic Reviews*, Issue 9. Art. No.: CD004923. http://dx.doi.org/10.1002/14651858.CD004923.pub2.
34. Daley, A., Stokes-Lampard, H. & Macarthur, C. Exercise for vasomotor menopausal symptoms. *Cochrane Database of Systematic Reviews*, Issue 5. Art. No.: CD006108. http://dx.doi.org/10.1002/14651858.CD006108.pub3.
35. Leach, M. J. & Moore, V. Black cohosh (Cimicifuga spp) for menopausal symptoms. *Cochrane Database of Systematic Reviews*, Issue 9. CD007244. http://dx.doi.org/10.1002/14651858.CD007244.pub2.
36. Eden, J. A. Phytoestrogens for menopausal symptoms: a review. *Maturitas* **72**, 157–159 (2012).
37. Langer, R. D. Efficacy, safety, and tolerability of low-dose hormone therapy in managing menopausal symptoms. *J. Am. Board Fam. Med.* **22**, 563–573 (2009).
38. Reginster, J. Y. *et al.* Effect of transdermal 17β-estradiol and oral conjugated equine estrogens on biochemical parameters of bone resorption in natural menopause. *Calcif. Tissue Int.* **53**, 13–16 (1993).
39. Wells, G. *et al.* Meta-analyses of therapies for postmenopausal osteoporosis. V. Meta-analysis of the efficacy of hormone replacement therapy in treating and preventing osteoporosis in postmenopausal women. *Endocr. Rev.* **23**, 529–539 (2002).
40. Cummings, S. R. *et al.* The effects of tibolone in older postmenopausal women. *N. Engl. J. Med.* **359**, 697–708 (2008).
41. Nelson, H. D., Walker, M., Zakher, B. & Mitchell, J. Menopausal hormone therapy for the primary prevention of chronic conditions: a systematic review to update the U. S. Preventive Services Task Force recommendations. *Ann. Intern. Med.* **157**, 104–113 (2012).
42. Cauley, J. *et al.* Effects of estrogen plus progestin on risk of fracture and bone mineral density: the Women's Health Initiative randomized trial. *JAMA* **290**, 1729–1738 (2003).
43. Anderson, G. L. *et al.* Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA* **291**, 1701–1712 (2004).
44. Santen, R. J. *et al.* Postmenopausal hormone therapy: an Endocrine Society scientific statement. *J. Clin. Endocrinol. Metab.* **95** (Suppl. 1), S1–S66 (2010).
45. MacLean, C. *et al.* Systematic review: comparative effectiveness of treatments to prevent fractures in men and women with low bone density or osteoporosis. *Ann. Intern. Med.* **148**, 197–213 (2008).
46. Body, J. J. *et al.* Evidence-based guidelines for the pharmacological treatment of postmenopausal osteoporosis: a consensus document by the Belgian Bone Club. *Osteoporos. Int.* **21**, 1657–1680 (2010).
47. Anderson, G. L. *et al.* Conjugated equine oestrogen and breast cancer incidence and mortality in postmenopausal women with hysterectomy: extended follow-up of the Women's Health Initiative randomised placebo-controlled trial. *Lancet Oncol.* **13**, 476–486 (2012).
48. Nappi, R. E. & Kokot-Kierepa, M. Women's voices in the menopause: results from an international survey on vaginal atrophy. *Maturitas* **67**, 233–238 (2010).
49. Lynch, C. Vaginal estrogen therapy for the treatment of atrophic vaginitis. *J. Womens Health (Larchmt)* **18**, 1595–1606 (2009).
50. Bachmann, G. A., Komi J. O. & Ospemifene Study Group. Ospemifene effectively treats vulvovaginal atrophy in postmenopausal women: results from a pivotal phase 3 study. *Menopause* **17**, 480–486 (2010).
51. Cody, J. D., Jacobs, M. L, Richardson, K., Moehrer, B. & Hextall, A. Oestrogen therapy for urinary incontinence in post-menopausal women. *Cochrane Database of Systematic Reviews*, Issue 10. Art. No.: CD001405. http://dx.doi.org/10.1002/14651858.CD001405.pub3.
52. Ismail, S. I., Bain, C. & Hagen, S. Oestrogens for treatment or prevention of pelvic organ prolapse in postmenopausal women. *Cochrane Database of Systematic Reviews*, Issue 9. Art. No.: CD007063. http://dx.doi.org/10.1002/14651858.CD007063.pub2.
53. Col, N. F. *et al.* Patient-specific decisions about hormone replacement therapy in postmenopausal women. *JAMA* **277**, 1140–1147 (1997).
54. Sullivan, J. M., El-Zeky, F., Vander Zwaag, R. & Ramanathan, K. B. Effect on survival of estrogen replacement therapy after coronary artery bypass grafting. *Am. J. Cardiol.* **79**, 847–850 (1997).
55. Grodstein, F. & Stampfer, M. J. Estrogen for women at varying risk of coronary disease. *Maturitas* **30**, 19–26 (1998).
56. Marjoribanks, J., Farquhar, C., Roberts, H. & Lethaby, A. Long term hormone therapy for perimenopausal and postmenopausal women. *Cochrane Database of Systematic Reviews* Issue 7. Art. No.: CD004143. http://dx.doi.org/10.1002/14651858.CD004143.pub4.
57. Hodis, H. N. *et al.* Estrogen in the prevention of atherosclerosis: a randomized, double-blind, placebo-controlled trial. *Ann. Intern. Med.* **135**, 939–953 (2001).
58. Hodis, H. N. *et al.* Hormone therapy and the progression of coronary-artery atherosclerosis in postmenopausal women. *N. Engl. J. Med.* **349**, 535–545 (2003).
59. Manson, J. E. *et al.* Estrogen therapy and coronary-artery calcification. *N. Engl. J. Med.* **356**, 2591–2602 (2007).
60. Mendelsohn, M. E. & Karas, R. H. HRT and the young at heart. *N. Engl. J. Med.* **356**, 2639–2641 (2007).
61. Hernán, M. A. *et al.* Observational studies analyzed like randomized experiments: an application to postmenopausal hormone therapy and coronary heart disease. *Epidemiology* **19**, 766–779 (2008).
62. Hodis, H. N. & Mack, W. J. A "window of opportunity:" the reduction of coronary heart disease and total mortality with menopausal therapies is age- and time-dependent. *Brain Res.* **1379**, 244–252 (2011).
63. Tuomikoski, P., Ylikorkala, O. & Mikkola T. S. Menopausal hot flushes and vascular health. *Ann. Med.* **43**, 283–291 (2011).
64. Schierbeck, L. L. *et al.* Effect of hormone replacement therapy on cardiovascular events in recently postmenopausal women: randomised trial. *BMJ* **345**, e6409 (2012).
65. Lobo, R. A. & Clarkson, T. B. Different mechanisms for benefit and risk of coronary heart disease and stroke in early postmenopausal women: a hypothetical explanation. *Menopause* **18**, 237–240 (2011).
66. Bath, P. M. & Gray, L. J. Association between hormone replacement therapy and subsequent stroke: a meta-analysis. *BMJ* **330**, 342 (2005).
67. Sare, G. M., Gray, L. J. & Bath, P. M. Association between hormone replacement therapy and subsequent arterial and venous vascular events: a meta-analysis. *Eur. Heart J.* **29**, 2031–2041 (2008).
68. Grodstein, F., Manson, J. E., Stampfer, M. J. & Rexrode, K. Postmenopausal hormone therapy and stroke: role of time since menopause and age at initiation of hormone therapy. *Arch. Intern. Med.* **168**, 861–866 (2008).
69. Renoux, C., Dell'aniello, S., Garbe, E. & Suissa, S. Hormone replacement therapy use and the risk of stroke. *Maturitas* **61**, 305–309 (2008).
70. Sweetland, S. *et al.* Venous thromboembolism risk in relation to use of different types of postmenopausal hormone therapy in a large prospective study. *J. Thromb. Haemost.* http://dx.doi.org/10.1111/j.1538-7836.2012.04919.x.
71. Canonico, M., Plu-Bureau, G., Lowe, G. D. & Scarabin, P. Y. Hormone replacement therapy and risk of venous thromboembolism in postmenopausal women: systematic review and meta-analysis. *BMJ* **336**, 1227–1231 (2008).
72. Olié, V., Canonico, M. & Scarabin, P. Y. Risk of venous thrombosis with oral versus transdermal estrogen therapy among postmenopausal women. *Curr. Opin. Hematol.* **17**, 457–463 (2010).
73. Tremollieres, F. *et al.* EMAS position statement: managing menopausal women with a personal or family history of VTE. *Maturitas* **69**, 195–198 (2011).
74. Anderson, G. L. *et al.* Prior hormone therapy and breast cancer risk in the Women's Health Initiative randomized trial of estrogen plus progestin. *Maturitas* **55**, 103–115 (2006).
75. Chlebowski, R. T. *et al.* Estrogen plus progestin and breast cancer incidence and mortality in

postmenopausal women. *JAMA* **304**, 1684–1692 (2010).
76. Fournier, A., Mesrine, S., Boutron-Ruault, M. C. & Clavel-Chapelon, F. Estrogen–progestagen menopausal hormone therapy and breast cancer: does delay from menopause onset to treatment initiation influence risks? *J. Clin. Oncol.* **27**, 5138–5143 (2009).
77. Lyytinen, H., Pukkala, E. & Ylikorkala, O. Breast cancer risk in postmenopausal women using estradiol–progestogen therapy. *Obstet. Gynecol.* **113**, 65–73 (2009).
78. Prentice, R. L. *et al.* Estrogen plus progestin therapy and breast cancer in recently postmenopausal women. *Am. J. Epidemiol.* **167**, 1207–1216 (2008).
79. Prentice, R. L. *et al.* Conjugated equine estrogens and breast cancer risk in the Women's Health Initiative clinical trial and observational study. *Am. J. Epidemiol.* **167**, 1407–1415 (2008).
80. Beral, V., Reeves, G., Bull, D., Green J. & Million Women Study Collaborators. Breast cancer risk in relation to the interval between menopause and starting hormone therapy. *J. Natl Cancer Inst.* **103**, 296–305 (2011).
81. Crandall, C. J. *et al.* Breast tenderness and breast cancer risk in the estrogen plus progestin and estrogen-alone Women's Health Initiative clinical trials. *Breast Cancer Res. Treat.* **132**, 275–285 (2012).
82. Couto, E. *et al.* Hormone therapy use and mammographic density in postmenopausal Norwegian women. *Breast Cancer Res. Treat.* **132**, 297–305 (2012).
83. Chlebowski, R. T. *et al.* Breast cancer after use of estrogen plus progestin in postmenopausal women. *N. Engl. J. Med.* **360**, 573–587 (2009).
84. Grady, D., Gebretsadik, T., Kerlikowske, K., Ernster, V. & Petitti, D. Hormone replacement therapy and endometrial cancer risk: a meta-analysis. *Obstet. Gynecol.* **85**, 304–313 (1995).
85. Furness, S., Roberts, H., Marjoribanks, J. & Lethaby, A. Hormone therapy in postmenopausal women and risk of endometrial hyperplasia. *Cochrane Database of Systematic Reviews*, Issue 8. Art. No.: CD000402. http://dx.doi.org/10.1002/14651858.CD000402.pub4.
86. Skouby, S. O. *et al.* Climacteric medicine: European Menopause and Andropause Society (EMAS) 2004/2005 position statements on peri- and postmenopausal hormone replacement therapy. *Maturitas* **51**, 8–14 (2005).
87. Anderson, G. L. *et al.* Effects of estrogen plus progestin on gynecologic cancers and associated diagnostic procedures: the Women's Health Initiative randomized trial. *JAMA* **290**, 1739–1748 (2003).
88. Greiser, C. M., Greiser, E. M. & Dören, M. Menopausal hormone therapy and risk of ovarian cancer: systematic review and meta-analysis. *Hum. Reprod. Update* **13**, 453–463 (2007).
89. Pearce, C. L., Chung, K., Pike, M. C. & Wu, A. H. Increased ovarian cancer risk associated with menopausal estrogen therapy is reduced by adding a progestin. *Cancer* **115**, 531–539 (2009).
90. Mørch, L. S., Løkkegaard, E., Andreasen, A. H., Kjaer, S. K. & Lidegaard, O. Hormone therapy and different ovarian cancers: a national cohort study. *Am. J. Epidemiol.* **175**, 1234–1242 (2012).
91. National Cancer Institute. *Seer Stats Fact Sheet: Ovary* [online], http://seer.cancer.gov/statfacts/html/ovary.html#risk (2012).
92. Grodstein, F., Newcomb, P. A. & Stampfer, M. J. Postmenopausal hormone therapy and the risk of colorectal cancer: a review and meta-analysis. *Am. J. Med.* **106**, 574–582 (1999).
93. Simon, M. S. *et al.* Estrogen plus progestin and colorectal cancer incidence and mortality. *J. Clin. Oncol.* **30**, 3983–3990 (2012).
94. Chlebowski, R. T. *et al.* Lung cancer among postmenopausal women treated with estrogen alone in the Women's Health Initiative randomized trial. *J. Natl Cancer Inst.* **102**, 1413–1421 (2010).
95. Chlebowski, R. T. *et al.* Oestrogen plus progestin and lung cancer in postmenopausal women (Women's Health Initiative trial): a post-hoc analysis of a randomised controlled trial. *Lancet* **374**, 1243–1251 (2009).
96. Antoine, C. *et al.* Safety of hormone therapy after breast cancer: a qualitative systematic review. *Hum. Reprod.* **22**, 616–622 (2007).
97. von Schoultz, E., Rutqvist L. E. & Stockholm Breast Cancer Study Group. Menopausal hormone therapy after breast cancer: the Stockholm randomized trial. *J. Natl Cancer Inst.* **97**, 533–535 (2005).
98. Holmberg, L., Anderson, H. & HABITS steering and data monitoring committees. HABITS (hormonal replacement therapy after breast cancer—is it safe?), a randomised comparison: trial stopped. *Lancet* **363**, 453–455 (2004).
99. Holmberg, L. *et al.* Increased risk of recurrence after hormone replacement therapy in breast cancer survivors. *J. Natl Cancer Inst.* **100**, 475–482 (2008).
100. Kenemans, P. *et al.* Safety and efficacy of tibolone in breast-cancer patients with vasomotor symptoms: a double-blind, randomised, non-inferiority trial. *Lancet Oncol.* **10**, 135–146 (2009).
101. Fahlén, M. *et al.* Hormone replacement therapy after breast cancer: 10 year follow up of the Stockholm randomised trial. *Eur. J. Cancer* **49**, 52–59 (2013).
102. Antoine, C. *et al.* A survey among breast cancer survivors: treatment of the climacteric after breast cancer. *Climacteric* **11**, 322–328 (2008).
103. Kendall, A., Dowsett, M., Folkerd, E. & Smith, I. Caution: vaginal estradiol appears to be contraindicated in postmenopausal women on adjuvant aromatase inhibitors. *Ann. Oncol.* **17**, 584–587 (2006).
104. Hickey, M. *et al.* Practical clinical guidelines for assessing and managing menopausal symptoms after breast cancer. *Ann. Oncol.* **19**, 1669–1680 (2008).
105. Bordeleau, L., Pritchard, K., Goodwin, P. & Loprinzi, C. Therapeutic options for the management of hot flashes in breast cancer survivors: an evidence-based review. *Clin. Ther.* **29**, 230–241 (2007).
106. Chapman, J. A. *et al.* Estrogen replacement in surgical stage I and II endometrial cancer survivors. *Am. J. Obstet. Gynecol.* **175**, 1195–1200 (1996).
107. Suriano, K. A. *et al.* Estrogen replacement therapy in endometrial cancer patients: a matched control study. *Obstet. Gynecol.* **97**, 555–560 (2001).
108. Barakat, R. R. *et al.* Randomized double-blind trial of estrogen replacement therapy versus placebo in stage I or II endometrial cancer: a Gynecologic Oncology Group Study. *J. Clin. Oncol.* **24**, 587–592 (2006).
109. Rozenberg, S. & Vasquez, J. B. Estrogen replacement therapy in patients with endometrial cancer: prescription attitude of Belgian gynecologists. *Maturitas* **35**, 125–128 (2000).
110. Maxwell, G. L. *et al.* Racial disparities in recurrence among patients with early-stage endometrial cancer: is recurrence increased in black patients who receive estrogen replacement therapy? *Cancer* **113**, 1431–1437 (2008).
111. Biglia, N., Gadducci, A., Ponzone, R., Roagna, R. & Sismondi, P. Hormone replacement therapy in cancer survivors. *Maturitas* **48**, 333–346 (2004).
112. Guidozzi, F. & Daponte, A. Estrogen replacement therapy for ovarian cancer survivors: a randomized controlled trial. *Cancer* **86**, 1013–1018 (1999).
113. Ovarian Cancer Canada. *Treatment and recovery, surgery* [online], http://www.ovariancanada.org/KnowledgeAwareness/Treatment-And-Recovery/Surgery (2012).
114. Barrett-Connor, E. & Laughlin, G. A. Endogenous and exogenous estrogen, cognitive function, and dementia in postmenopausal women: evidence from epidemiologic studies and clinical trials. *Semin. Reprod. Med.* **27**, 275–282 (2009).
115. Henderson, V. W. Aging, estrogens, and episodic memory in women. *Cogn. Behav. Neurol.* **22**, 205–214 (2009).
116. Hogervorst, E. & Bandelow, S. Sex steroids to maintain cognitive function in women after the menopause: a meta-analyses of treatment trials. *Maturitas* **66**, 56–71 (2010).
117. Silverman, D. H. *et al.* Differences in regional brain metabolism associated with specific formulations of hormone therapy in postmenopausal women at risk for AD. *Psychoneuroendocrinology* **36**, 502–513 (2011).
118. Shao, H. *et al.* Hormone therapy and Alzheimer disease dementia: new findings from the Cache County Study. *Neurology* **79**, 1846–1852 (2012).
119. Shumaker, S. A. *et al.* Conjugated equine estrogens and incidence of probable dementia and mild cognitive impairment in postmenopausal women: Women's Health Initiative Memory Study. *JAMA* **291**, 2947–2958 (2004).
120. Hays, J. *et al.* Effects of estrogen plus progestin on health-related quality of life. *N. Engl. J. Med.* **348**, 1839–1854 (2003).
121. Brunner, R. L. *et al.* Effects of conjugated equine estrogen on health-related quality of life in postmenopausal women with hysterectomy: results from the Women's Health Initiative randomized clinical trial. *Arch. Intern. Med.* **165**, 1976–1986 (2005).
122. Nielsen, T. F., Ravn, P., Pitkin, J. & Christiansen, C. Pulsed estrogen therapy improves postmenopausal quality of life: a 2-year placebo-controlled study. *Maturitas* **53**, 184–190 (2006).
123. Rossouw, J. E. *et al.* Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA* **288**, 321–333 (2002).
124. Cauley, J. A. *et al.* Estrogen replacement therapy and mortality among older women. The study of osteoporotic fractures. *Arch. Intern. Med.* **157**, 2181–2187 (1997).
125. Paganini-Hill, A., Corrada, M. M. & Kawas, C. H. Increased longevity in older users of postmenopausal estrogen therapy: the Leisure World Cohort Study. *Menopause* **13**, 12–18 (2006).
126. Ryan, J. *et al.* Hormone treatment, estrogen receptor polymorphisms and mortality: a prospective cohort study. *PLoS ONE* **7**, e34112 (2012).
127. Moyer, V. A & on behalf of the U.S. Preventive Services Task Force. Menopausal hormone therapy for the primary prevention of chronic conditions: U. S. Preventive Services Task Force Recommendation Statement. *Ann. Intern. Med.* **158**, 47–54 (2013).

128. Shuster, L. T., Gostout, B. S., Grossardt, B. R. & Rocca, W. A. Prophylactic oophorectomy in premenopausal women and long-term health. *Menopause Int.* **14**, 111–116 (2008).
129. Vujovic, S. *et al.* EMAS position statement: managing women with premature ovarian failure. *Maturitas* **67**, 91–93 (2010).
130. Sim, L. A. *et al.* Effect on bone health of estrogen preparations in premenopausal women with anorexia nervosa: a systematic review and meta-analyses. *Int. J. Eat. Disord.* **43**, 218–225 (2010).
131. Kanis, J. A. *et al.* Development and use of FRAX in osteoporosis. *Osteoporos. Int.* **21** (Suppl. 2), S407–S413 (2010).
132. Rockhill, B., Spiegelman, D., Byrne, C., Hunter, D. J. & Colditz G. A. Validation of the Gail *et al.* model of breast cancer risk prediction and implications for chemoprevention. *J. Natl Cancer Inst.* **93**, 358–366 (2001).
133. Tyrer, J., Duffy, S. W. & Cuzick, J. A breast cancer prediction model incorporating familial and personal risk factors. *Stat. Med.* **23**, 1111–1130 (2004).
134. Pencina, M. J., D'Agostino, R. B. Sr, Larson, M. G., Massaro, J. M. & Vasan, R. S. Predicting the 30-year risk of cardiovascular disease: the Framingham heart study. *Circulation* **119**, 3078–3084 (2009).
135. Ridker, P. M., Buring, J. E., Rifai, N. & Cook, N. R. Development and validation of improved algorithms for the assessment of global cardiovascular risk in women: The Reynolds Risk Score. *JAMA* **297**, 611–619 (2007).
136. Collins, G. S. & Altman, D. G. An independent and external validation of QRISK2 cardiovascular disease risk score: a prospective open cohort study. *BMJ* **340**, c2442 (2010).
137. Perk, J. *et al.* European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur. Heart J.* **33**, 1635–1701 (2012).
138. Hippisley-Cox, J. & Coupland, C. A. Development and validation of a risk prediction algorithm (QThrombosis) to estimate future risk of venous thromboembolism: prospective cohort study. *BMJ* **343**, d4656 (2011).
139. Billon-Galés, A. *et al.* Activation function 2 (AF2) of estrogen receptor-α is required for the atheroprotective action of estradiol but not to accelerate endothelial healing. *Proc. Natl Acad. Sci. USA* **108**, 13311–13316 (2011).
140. Mackey, R. H. *et al.* Hormone therapy, estrogen metabolism, and risk of breast cancer in the Women's Health Initiative Hormone Therapy Trial. *Cancer Epidemiol. Biomarkers Prev.* **20**, 2022–2032 (2012).
141. Huang, Y. *et al.* Exploring the interaction between SNP genotype and postmenopausal hormone therapy effects on stroke risk. *Genome Med.* **4**, 57 (2012).

Acknowledgements
Research funding received from Amgen, IRIS, King Baudouin Foundation, MSD and Vesale research Foundation.

Author contributions
S. Rozenberg researched data for the article, contributed to discussion of the content, wrote the article and reviewed/edited the manuscript before submission. J. Vandromme and C. Antoine contributed to discussion of the content and reviewed/edited the manuscript before submission.

Supplementary information is linked to the online version of the paper at www.nature.com/nrendo.