

# Risks and benefits of hormone replacement therapy: The evidence speaks

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## Abstract

UNTIL RECENTLY, OBSERVATIONAL STUDIES suggested a decreased risk of cardiovascular disease, osteoporotic fractures, cognitive decline and colon cancer with the use of hormone replacement therapy (HRT). Recent randomized controlled trials have failed to show a protective effect of HRT in reducing the risk of coronary artery disease and instead have revealed an increased risk of heart disease, stroke, invasive breast cancer and venous thromboembolism, but a decreased risk of colorectal cancer and osteoporotic fractures. In this article we review the current evidence of the risks and benefits of HRT.

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## Case

Ms. R is a 55-year-old postmenopausal woman with a 6-month history of hot flashes, particularly at night, resulting in sleep disturbances, and vaginal dryness. Bone mineral density testing showed osteopenia of the lumbar spine and normal bone density of the femur. She has no history of fractures. She has dyslipidemia (total cholesterol level 5.80 mmol/L, low-density lipoprotein cholesterol level 3.90 mmol/L, high-density lipoprotein cholesterol level 1.10 mmol/L and triglyceride level 2.20 mmol/L) and hypertension but is a nonsmoker and has no history of diabetes mellitus. She has a history of fibrocystic breast disease and has undergone 2 biopsy procedures, with no evidence of atypical hyperplasia or malignant disease. Her past history is otherwise unremarkable. Her mother received a diagnosis of metastatic breast cancer at age 60 years. Coronary artery disease was diagnosed in her father at age 55 years, and at age 60 he experienced a stroke. Her 2 siblings, both younger, are well. She is considering use of hormone replacement therapy.

There are over 4.6 million Canadian women 50 years of age or older, for whom hormone replacement therapy (HRT) may be a consideration. The evidence to support the use of estrogen replacement therapy for the treatment of vasomotor symptoms (hot flashes, night sweats, sleep disturbances)<sup>1</sup> and urogenital symptoms (vaginal dryness, urogenital atrophy)<sup>2</sup> is based on clinical trial data. However, support for the use of HRT to prevent cardiovascular disease, osteoporotic fractures, colon cancer and dementia is controversial and until recently was based in large part on observational trials. Despite 50 years of use of HRT, data from randomized controlled trials (RCTs) of HRT for the prevention of chronic disease in postmenopausal women have only recently been published. These tri-

als provide important data that contradict conclusions based on observational studies and raise questions about the short-term risks and long-term benefits of HRT in this population. In this review, we examine the benefits and risks of HRT use, emphasizing RCT data whenever these are available, and offer an approach to advising use of HRT. Our literature search strategy is described in Appendix 1.

## Impact of hormone replacement therapy

### Cardiovascular disease

Coronary artery disease (CAD) is the leading cause of death and disability among women in Canada. Meta-analyses of the Nurses' Health Study and other observational studies suggested that HRT reduces the risk of CAD in postmenopausal women by 35%–50%<sup>3-5</sup> (Fig. 1), and evidence from several sources suggests that estrogen is cardioprotective.<sup>6-9</sup>

Five clinical end-point trials of HRT for cardiovascular disease have been completed and reported. The Heart and Estrogen/progestin Replacement Study (HERS)<sup>10</sup> was the first large randomized placebo-controlled clinical trial of estrogen for secondary prevention of CAD in postmenopausal women. In contrast to the observational evidence, there was no clinical benefit associated with the use of HRT (relative risk [RR] 0.99, 95% confidence interval [CI] 0.80–1.22), despite the presence of favourable lipid effects. The high risk of primary CAD events observed in the first year decreased in subsequent years, a significant time trend ( $p_{\text{trend}} = 0.009$ ). This finding led to speculation that the duration of the HERS was too short to demonstrate the putative beneficial effects of HRT. However, the recently published results of HERS II,<sup>11</sup> with 6.8 years of follow-up, confirmed the finding of the first trial: HRT does not decrease the risk of cardiovascular disease in women with CAD (RR 0.99, 95% CI 0.84–1.17) (Fig. 2).

Another secondary-prevention clinical end-point trial, the Women's Estrogen for Stroke Trial,<sup>12</sup> failed to show any benefit of HRT in lowering the risk of death or nonfatal stroke (RR 1.1, 95% CI 0.8–1.4). Similarly, the secondary analysis of the HERS showed no reduction in the risk of stroke (RR 1.23, 95% CI 0.89–1.70).<sup>13</sup>

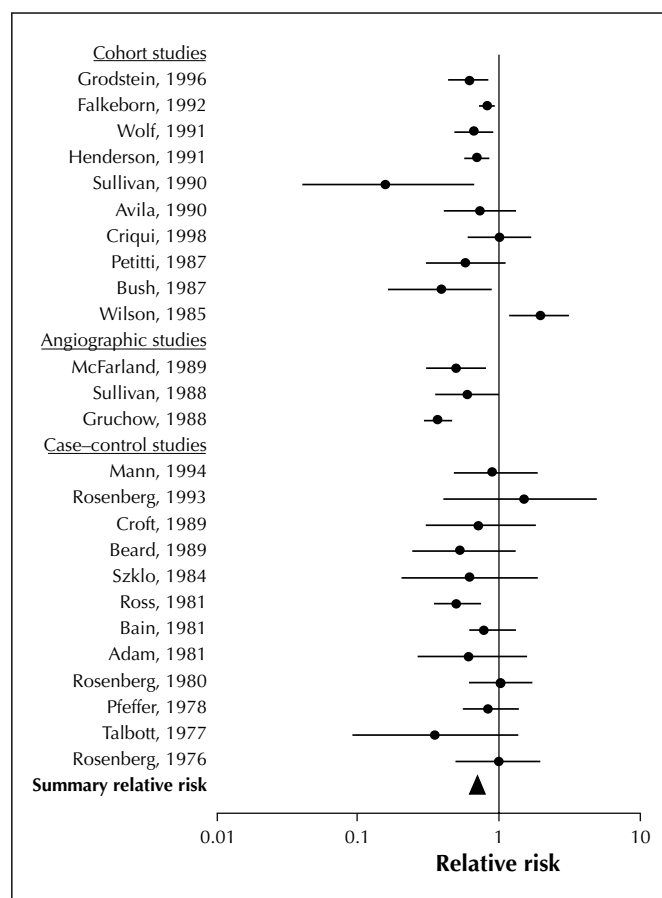
The recently published Women's Health Initiative (WHI) trial,<sup>14</sup> a primary prevention trial of HRT in postmenopausal women, also failed to demonstrate any benefit of

HRT for the prevention of CAD (RR 1.29, 95% CI 0.85–1.97) or stroke (RR 1.41, 95% CI 0.86–2.31) after 5.2 years of follow-up (Fig. 3). These results pertain to the estrogen plus progestin arm of the study. The unopposed estrogen arm, involving women without an intact uterus, is scheduled to continue until 2005.

It has been suggested that more favourable results may be obtained with other preparations of estrogen.<sup>14</sup> However, the Papworth HRT atherosclerosis study,<sup>15</sup> a secondary prevention trial of transdermal HRT, also failed to demonstrate a reduced risk of hospital admission because of unstable angina, myocardial infarction or death from cardiac causes in postmenopausal women. The event rate per 100 patient-years in the HRT group was 15.4, as compared with 11.9 in the control group (RR 1.29, 95% CI 0.84–1.95).

The favourable lipid results in the HERS and the WHI trial mirrored those reported in 4 surrogate end-point trials: the Postmenopausal Estrogen/Progestin Interventions (PEPI) trial,<sup>16</sup> the Estrogen Replacement and Atherosclerosis (ERA) trial,<sup>17</sup> the Estrogen in the Prevention of Atherosclerosis Trial (EPAT)<sup>18</sup> and the Women's Angiographic Vita-

min and Estrogen (WAVE) Trial.<sup>19</sup> The ERA and WAVE trials failed to show a significant reduction in progression of coronary atherosclerosis, unlike the EPAT, which did show a slower rate of progression of clinically unapparent atherosclerosis in healthy postmenopausal women. It is difficult to compare the results of these surrogate end-point trials given the different populations (secondary prevention in the ERA and WAVE trials, primary prevention in the EPAT and the PEPI trial), different end points (lipid changes in the PEPI trial, coronary artery diameter in the ERA and WAVE trials, intima media thickness in the EPAT) and different HRT preparations (conjugated equine estrogen plus medroxyprogesterone acetate in the PEPI, WAVE and ERA trials, estradiol-17 $\beta$  in the EPAT). The only consistent finding was an increase in levels of high-density lipoprotein cholesterol and a decrease in levels of low-density lipoprotein cholesterol in women receiving HRT. These favourable lipid changes do not, however, appear to translate into clinical benefit based on the results of the clinical end-point RCTs. The latter are summarized in Table 1; the surrogate end-point trials are summarized in an online table available at [www.cmaj.ca](http://www.cmaj.ca).



**Fig. 1: Meta-analysis of observational studies of the risk of coronary artery disease in postmenopausal women taking estrogen and those not taking estrogen, published up to mid-1997. Reprinted, with permission, from reference 3. Copyright 1998, Annual Reviews.**

## Summary

Despite consistent results from numerous observational trials and strong biologic plausibility, evidence from clinical trials does not support the hypothesis that HRT reduces the risk of cardiovascular disease. The American Heart Association issued a statement on HRT and cardiovascular disease in mid-2001.<sup>20</sup> In its summary recommendations, the association concluded that HRT should not be prescribed for the *secondary prevention* of cardiovascular disease. Recent evidence from the WHI trial also fails to support the use of HRT for the *primary prevention* of CAD. The efficacy of unopposed estrogen for primary prevention is still being investigated in the ongoing WHI study.

## Osteoporosis

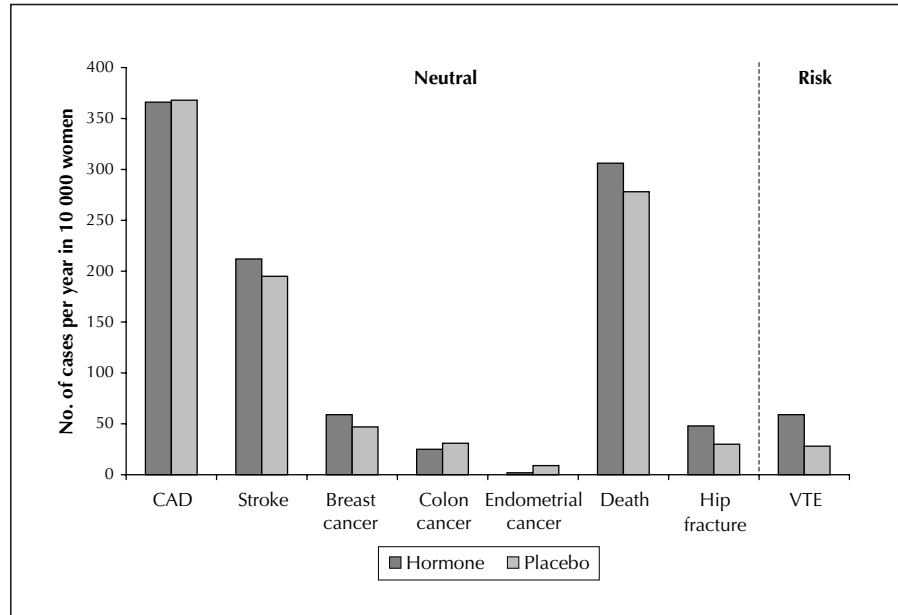
Osteoporosis has a significant effect on morbidity and mortality in the aging population, affecting about 1 in 4 postmenopausal women. There is ample evidence of increased bone mineral density in postmenopausal women receiving HRT compared with those receiving placebo.<sup>21</sup> In a randomized placebo-controlled trial involving frail elderly women, who are particularly susceptible to fractures, a 9-month course of HRT (conjugated equine estrogen [0.625 mg/d] plus medroxyprogesterone acetate [5 mg/d] for 13 days per month) increased bone mineral density in the lumbar spine (3.9%, 95% CI 3.5%–4.3%) and hip (1.8%, 95% CI 1.5%–2.1%).<sup>22</sup> However, clinical trial data supporting HRT for reducing fracture risk are inconsistent and limited.

There are few trials demonstrating fracture risk reduction with estrogen therapy (Table 2). One clinical trial indicated a reduction of about 60% per 100 patient-years in the rate of vertebral fractures among postmenopausal women with es-

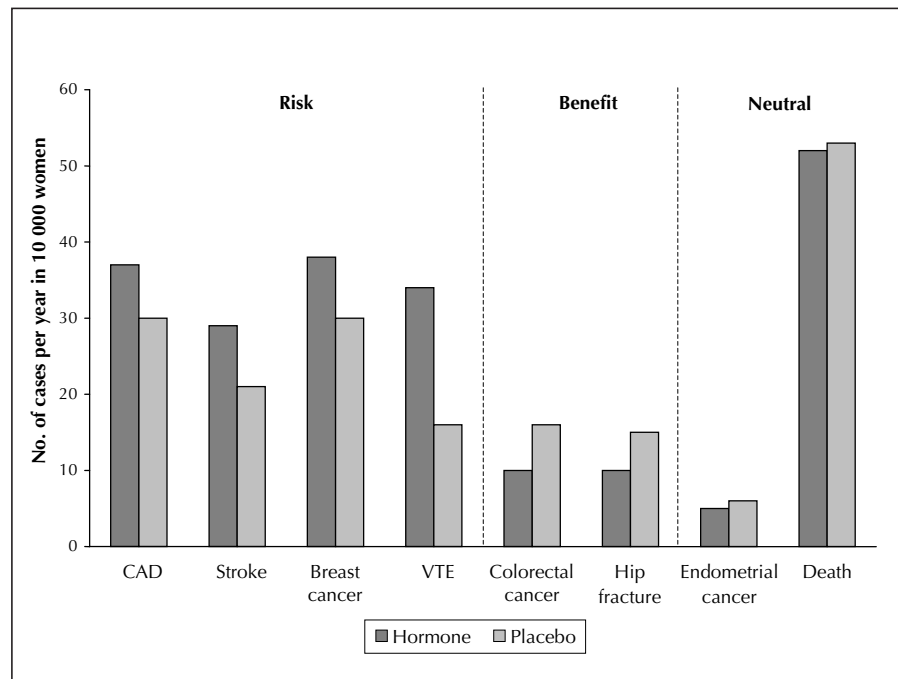
tablished osteoporosis who were given HRT.<sup>23</sup> However, the unit of observation was the total number of fractures instead of the number of women with fractures. When the numbers of women affected with new fractures were compared, the effect of HRT was no longer found to be statistically significant.<sup>29</sup> Similarly, the HERS<sup>27</sup> and HERS II<sup>28</sup> indicated no difference in the incidence of fractures between women receiving HRT and those receiving placebo after 4.1 and 6.8 years respectively (Fig. 2). It should be noted that fractures were a secondary outcome in these studies, which were neither designed nor powered to assess osteoporosis in this population.

The recently published primary results of the WHI trial<sup>14</sup> do support the ability of HRT to prevent overall fractures of the hip (Fig. 3), vertebrae and other sites (RR 0.76, 95% CI 0.63–0.92). Again, fractures were a secondary outcome, and the results should be interpreted with caution.

There are no data from randomized prospective trials evaluating the effect of HRT on nonvertebral fractures as the primary outcome. In a recent meta-analysis of 22 trials assessing the risk of nonvertebral fractures with HRT compared with no HRT, pooled analysis showed a reduction of 27% in the incidence of nonvertebral fractures in the HRT group (RR 0.73, 95% CI 0.56–0.94); however, many of the studies did not verify fractures radiographically.<sup>30</sup> The risk reduction appeared to be greater among women under 60 years of age (RR 0.67, 95% CI 0.46–0.98). However, this age-based dichotomy may be attributable to bias introduced by the large number of younger subjects in a few trials that affected the pooled data. When the data for hip and wrist fractures were assessed, HRT remained significantly effective (RR 0.60, 95% CI 0.40–0.91). Although there is some publication bias in favour of a positive response to HRT, the meta-analysis results were based on analyses from both unpublished and published data and remained supportive of nonvertebral fracture reduction.<sup>30</sup>



**Fig. 2: Effect of hormone replacement therapy (HRT) on cardiovascular and noncardiovascular outcomes among postmenopausal women with coronary artery disease (CAD) in the Heart and Estrogen/progestin Replacement Study (HERS) and HERS II (longer follow-up).<sup>11,28</sup> Venous thromboembolism (VTE) was the only outcome on which HRT had a significant effect compared with placebo.**



**Fig. 3: Effect of HRT on cardiovascular and noncardiovascular outcomes among healthy postmenopausal women in the Women’s Health Initiative trial.<sup>14</sup> Outcomes are grouped according to whether HRT had a negative or positive effect, or no effect, compared with placebo. [Source: WHI HRT Update — 2002, National Heart, Lung, and Blood Institute (National Institutes of Health, US Department of Health and Human Services), Bethesda, Md. (available [www.nhlbi.nih.gov/health/women/upd2002.htm](http://www.nhlbi.nih.gov/health/women/upd2002.htm) [accessed 2003 Mar 19]).**

## Summary

HRT has been shown to increase bone mineral density, but data supporting reduction of vertebral and nonvertebral osteoporotic fractures with HRT are inconsistent. Consequently, the US Food and Drug Administration indicates HRT for the prevention, not the treatment, of osteoporosis.<sup>31</sup> Similarly, the Scientific Advisory Council of the Osteoporosis Society of Canada recommends HRT as first-line preventive therapy in postmenopausal women who have low bone density but as second-line treatment in postmenopausal women who have osteoporosis.<sup>32</sup> Alternatively, there are considerable data demonstrating vertebral and nonvertebral fracture reduction with bisphosphonates,<sup>33,34</sup> and vertebral fracture reduction with selective estrogen-receptor modulators<sup>35</sup> and calcitonin.<sup>36</sup>

## Cognitive function and dementia

Postmenopausal women often experience a subjective sense of cognitive decline with increasing age, and those receiving HRT frequently report improvement in memory and cognition.<sup>37</sup> Results of observational studies have been mixed, some suggesting a benefit with HRT use, others showing no association. The recently published Cache County Study,<sup>38</sup> a longitudinal observational study of the prevalence and incidence of Alzheimer's disease and other forms of dementia, suggested that use of HRT for more than 10 years was associated with a significant decrease in the risk of Alzheimer's disease (hazard ratio 0.41, 95% CI 0.17–0.86).

Of the 7 published RCTs of estrogen therapy and cognition,<sup>39–45</sup> 6 suggested that estrogen therapy improved cognitive function.<sup>39–41,43–45</sup> However, the trials were small (16–84 subjects), 2 of the earlier trials used nonvalidated,

uncommon test instruments,<sup>44,45</sup> and 5 of the 6 studies that showed benefit included many recently menopausal women who experienced estrogen-deficiency symptoms.<sup>39–41,43,45</sup> Recently menopausal women are more likely than women who are well into menopause to report vasomotor symptoms and insomnia. Relief of these symptoms may have resulted in improved cognitive function. In summary, all these trials had substantial methodologic problems that create doubt about the efficacy of estrogen for improving cognitive performance in postmenopausal women.

Four small trials of estrogen therapy involving women with Alzheimer's disease showed improvement in some, but not all, measures of dementia severity.<sup>46–49</sup> However, 2 of the trials were uncontrolled and unblinded,<sup>46,47</sup> so the results can just as easily be explained as a practice or learning effect. The third trial, also unblinded, showed that women treated with conjugated equine estrogen had improved cognitive function and decreased dementia severity compared with baseline, whereas untreated women did not.<sup>48</sup> The fourth trial, both placebo-controlled and blinded, showed that women receiving conjugated equine estrogen had improved scores on the Hasegawa Dementia Scale, but there were no differences in the Mini-Mental Status Examination or the study-specific dementia test results between the treated and untreated groups.<sup>49</sup>

## Summary

Evidence supporting the role of HRT in the preservation of cognitive function in healthy postmenopausal women or for the treatment of Alzheimer's disease is weak. Large randomized placebo-controlled trials are needed to adequately assess the role of estrogen in preventing and treating Alzheimer's disease and other types of dementia.

**Table 1: Randomized controlled clinical end-point trials of hormone replacement therapy (HRT) for the prevention of cardiovascular disease**

Study	No. of subjects	Therapy	Mean duration, yr	End point(s)	Relative risk (and 95% CI)	Absolute risk/person-years*
<b>Secondary prevention</b>						
Heart and Estrogen/progestin Replacement Study (HERS) <sup>10</sup>	2 763	CEE + MPA	4.1	CAD-related death, nonfatal MI	0.99 (0.80–1.22)	–0.3/1000
				Thromboembolic event	2.89 (1.50–5.58)	3.9/1000
HERS II <sup>11</sup>	2 321	CEE + MPA	6.8	CAD-related death, nonfatal MI	0.99 (0.84–1.17)	–0.3/1000
				Thromboembolic event	2.08 (1.28–3.40)	1.5/1000
Women's Estrogen for Stroke Trial <sup>12</sup>	664	Estradiol-17β	3.0	Death, nonfatal stroke	1.1 (0.8–1.4)	6.7/1000
Papworth HRT atherosclerosis study <sup>15</sup>	225	Transdermal HRT	2.7	Cardiac death, MI, unstable angina	1.29 (0.84–1.95)	35/1000
<b>Primary prevention</b>						
Women's Health Initiative (WHI) trial <sup>14</sup>	16 608	CEE + MPA	5.2	CAD-related death, nonfatal MI	1.29 (0.85–1.97)	7/10 000

Note: CI = confidence interval, CEE = conjugated equine estrogen, MPA = medroxyprogesterone acetate, CAD = coronary artery disease, MI = myocardial infarction.

\*A negative value indicates a lower risk in the HRT group compared with placebo, and a positive value indicates a higher risk in the HRT group compared with placebo.



The Women's Health Initiative Memory Study<sup>50</sup> and the Women's Health Initiative Study on Cognitive Aging, to be completed in 2005, will provide important results to inform this debate, but at this time HRT is not indicated for the prevention of dementia.

### Breast cancer

Data on the association of breast cancer and HRT are inconsistent, and the magnitude of the risk is variable, depending on the HRT preparation, the dosage and the duration of therapy.<sup>51–54</sup> Several meta-analyses of observational studies have shown an increased risk of breast cancer with estrogen use (RR 1.06 to 1.3).<sup>53,55,56</sup> Analysis of original data from 51 epidemiologic studies involving 52 705 women with and 108 411 women without breast cancer revealed a significant increase in the relative risk of the disease associated with use of HRT (RR 1.14,  $p < 0.001$ ) compared with no history of use.<sup>54</sup> Therefore, for every 1000 women who start HRT at age 50 and use it for 10 years or 15 years, there are 6 (95% CI 3–9) and 12 (95% CI 5–20) excess cases of breast cancer respectively in the affected group, but without change in overall survival. It should be noted that observational data may underestimate the risk of breast cancer in women taking HRT, because the study populations prescribed HRT for the relief of menopausal symptoms and the prevention of osteoporosis consist of women who have lower estrogen levels, a population already at lower risk of

breast cancer. Conversely, observational data may also overestimate breast cancer risk, given the increased screening and early ascertainment of the diagnosis in these populations. The effect of this detection bias may be limited by the impaired sensitivity and specificity of mammography with increased breast tissue density among HRT users.<sup>57</sup>

Although the data on the effect of progestin therapy on the risk of breast cancer are limited, several observational studies support a relation between progestin use and increased breast cancer risk.<sup>58–61</sup> In a cohort of 46 355 postmenopausal women, after 4 years of use, combined estrogen and progesterone therapy was associated with a higher incidence of breast cancer than therapy with estrogen alone (RR 1.4 [95% CI 1.1–1.8] and 1.2 [95% CI 1.0–1.4] respectively).<sup>58</sup> The RR increased by 8% (95% CI 2%–16%) per year of use of estrogen plus progestin, compared with 1% (95% CI 2%–3%) per year of estrogen use alone.

The recently reported WHI trial<sup>14</sup> is the first RCT to confirm that the combination of estrogen plus progestin increases the risk of incident breast cancer (RR 1.26, 95% CI 0.83–1.92) (Fig. 3). As expected, the increased risk emerged several years after randomization. The excess incidence of breast cancer after 5.2 years of follow-up, 26%, is consistent with pooled estimates from observational studies (15%) and the nonsignificant increase found after 6.8 years of follow-up in the HERS II<sup>28</sup> (27%) (Fig. 2).

Women who have at least 1 first-degree relative with breast cancer are at increased risk of the disease.<sup>54</sup> HRT use

**Table 2: Randomized controlled end point trials of estrogen with or without progesterone and bone loss**

Investigator or study	Therapy	No. of subjects*	Mean duration, yr	End point(s)	Relative risk (and 95% CI)
Lufkin et al <sup>23</sup>	Estradiol-17 $\beta$ + MPA	75 women with vertebral fracture	1	Vertebral fracture	0.39 (0.16–0.95)
Wimalawansa <sup>24</sup>	CEE + MPA	72 women with osteoporosis	4	Vertebral fracture	0.40 (0.09–1.80)
Komulainen et al <sup>25</sup>	Estradiol + CYP Cholecalciferol Estradiol + CYP + cholecalciferol	464 women without osteoporosis	5	Nonvertebral fracture	0.29 (0.1–0.9) 0.47 (0.2–1.14) 0.44 (0.17–1.15)
Danish Osteoporosis Prevention Study <sup>26</sup>	Estradiol (cyclic administration) + NOR if uterus intact, OR estradiol (continuous administration) if hysterectomy	2016 healthy women without osteoporosis	5	All fractures Forearm fracture Vertebral fracture	0.86 (0.62–1.20) 0.43 (0.22–0.85) 1.25 (0.71–3.28)
HERS <sup>27</sup>	CEE + MPA	2 763 women with CAD, with or without osteoporosis	4.1	Fracture of spine Hip fracture Wrist fracture Other fracture	0.69 (0.3–1.4) 1.09 (0.5–2.3) 1.01 (0.6–1.7) 0.91 (0.7–1.2)
HERS II <sup>28</sup>	CEE + MPA	2321 women with CAD, with or without osteoporosis	6.8	Fracture of spine Hip fracture Wrist fracture Any fracture	0.89 (0.53–1.50) 1.61 (0.97–2.66) 1.00 (0.65–1.53) 1.07 (0.89–1.29)
WHI trial <sup>14</sup>	CEE + MPA	16 608 women	5.2	Hip fracture Vertebral fracture Other fracture	0.66 (0.45–0.98) 0.66 (0.44–0.98) 0.77 (0.69–0.86)

Note: CYP = cyproterone acetate, NOR = norethindrone acetate.

\*Study subjects were all postmenopausal women with the exception of the Danish Osteoporosis Prevention Study.

in this population has been observed to be associated with increased risk of breast cancer in some<sup>56</sup> but not all<sup>62</sup> studies. Regardless, some physician organizations do not recommend HRT in this group.<sup>63</sup> Women who have *BRCA1* and *BRCA2* mutations have a lifetime risk of breast cancer of up to 70%–80%. The effect of HRT use on increased risk of breast cancer in this susceptible group is unknown.

Given concerns about the possible risk of breast cancer recurrence and the principle of doing no harm, HRT use traditionally has been contraindicated in patients who have a personal history of breast cancer. However, there is no clear evidence of estrogen-induced recurrence of breast cancer with HRT in this population. In addition, small case series and short-term observational studies of HRT use in women who have a personal history of breast cancer have not shown increased rates of disease recurrence or death.<sup>64–66</sup> Women treated for breast cancer may experience debilitating estrogen-deficiency symptoms, for which nonhormonal alternatives constitute the current standard of care. Patients unresponsive to these treatments are faced with the dilemma of using HRT. Pending results of large prospective randomized trials, short-term use of low-dose HRT currently may be considered in this population after other, nonhormonal treatments to control menopausal symptoms have been exhausted.<sup>67</sup>

### Summary

The use of HRT in women at risk of breast cancer is controversial. Data from recent randomized trials and significant observational evidence suggest an increased risk of breast cancer with HRT. Such evidence dictates current guidelines, in which use of HRT is contraindicated in women who have a personal history of, or are at high risk for, breast cancer. However, the WHI investigators found an increased risk in women regardless of their family history or other risk factors for breast cancer,<sup>14</sup> which suggests a cumulative effect of HRT exposure. Alternative therapeutic options, including clonidine, antidepressants<sup>68</sup> and localized vaginal estrogen therapy for menopausal symptoms,<sup>69</sup> bisphosphonates<sup>33,34</sup> and selective estrogen-receptor modulators<sup>35</sup> for osteoporosis, and statins for dyslipidemia,<sup>70</sup> warrant consideration. In addition, preventive therapy with lifestyle changes must be emphasized. If HRT is required, short-term use of low dosages with rigorous monitoring may be considered.

### Endometrial cancer

In an observational study, Grady and colleagues<sup>71</sup> found an increased risk of endometrial cancer with unopposed estrogen use (RR 2.3, 95% CI 2.1–2.5). This finding is confirmed by evidence from an RCT, which showed an increased incidence of endometrial hyperplasia with higher dosages of unopposed estrogen and longer duration of use.<sup>72</sup> Combined estrogen and progesterone therapy reduces endometrial hyperstimulation and has been found to be associ-

ated with significant reductions in rates of atypical endometrial lesions.<sup>72</sup> Cyclic progesterone therapy (more than 12 days per month) is as effective as continuous low-dose progesterone therapy, and various progestins (medroxyprogesterone acetate, micronized progesterone) are equally efficacious in reducing the risk of endometrial hyperplasia.<sup>73</sup>

### Summary

Unopposed estrogen therapy is associated with an increased risk of endometrial cancer. The addition of progesterone therapy is protective against the development of estrogen-induced endometrial hyperplasia. Continuous combined HRT or cyclic progesterone therapy for more than 10 days per month reduces the risk of endometrial cancer to a risk similar to that among nonusers of estrogen.

### Thromboembolism

Observational data are supported by results from recent randomized trials showing an increased risk of thromboembolism with HRT.<sup>14,28,74</sup> The HERS II<sup>28</sup> confirmed the increased risk of thromboembolism in women with CAD first observed in the HERS<sup>13</sup> (Fig. 2). The WHI trial<sup>14</sup> showed an increased risk of venous thromboembolism with HRT in healthy postmenopausal women (hazard ratio 2.11, 95% CI 1.26–3.55), with 34 and 16 events per 10 000 woman-years in the HRT and placebo groups respectively (Fig. 3, Table 3). A meta-analysis of studies of estrogen use and risk of venous thromboembolism showed a summary relative risk (combination of RCTs, case-control studies and cohort studies) of 2.14 (95% CI 1.64–2.81), whereas data from the 3 RCTs gave a relative risk estimate of 3.75 (95% CI 1.23–10.26).<sup>74</sup> Therefore, with an estimated baseline risk of venous thromboembolism of 1.3 per 10 000 woman-years,<sup>76</sup> an additional 3.2 events for the first 12 months and 1.2 events after 12 months would be expected with estrogen use.<sup>74</sup> A randomized placebo-controlled trial of estradiol plus norethindrone acetate in women with a history of venous thromboembolism showed that, compared with placebo, HRT use was associated with an increased risk of recurrence of venous thromboembolism (10.7% v. 2.3%).<sup>77</sup> Transdermal estrogen regimens have been found to lack the effect on coagulation factors and hemostasis that oral estrogen therapy demonstrates, which suggests that the former have a lower hypercoagulability effect.<sup>78,79</sup>

### Summary

Women receiving HRT, particularly those who have a history of venous thromboembolism or are at risk of thromboembolism, are at increased risk of venous thromboembolism. The WHI trial results also indicate an increased risk associated with HRT in otherwise healthy postmenopausal women.<sup>14</sup> Because the incidence of thromboembolism in healthy postmenopausal women is low, the absolute risk of

venous thromboembolism with HRT remains relatively small. However, the current consensus is to avoid HRT in women who have a history of thromboembolic events and to use HRT cautiously in women when they are at high risk of thromboembolism (e.g., during a long period of immobilization).<sup>80</sup> Since congenital thrombophilic disorders are uncommon, screening for such disorders before prescribing HRT has not been found to be cost-effective.<sup>81</sup>

### Other diseases

Evidence from an observational study<sup>82</sup> and randomized double-blinded placebo-controlled trials<sup>10,28</sup> indicates a 1.5- to 2-fold increased risk of gallbladder disease associated with HRT. However, gallbladder and biliary tract diseases were secondary outcomes in these trials, and the effects of other factors, such as history of cardiovascular disease and dietary history, on risk of gallbladder disease were not accounted for.

Recently, estrogen use has been associated with a low risk of colon cancer, although mechanisms remain unclear. A pooled analysis of observational studies showed a 30% reduction in colon carcinoma and colorectal polyps among current HRT users and a 12% reduction among women who had ever received HRT.<sup>83</sup> This protective effect dissipated with cessation of HRT.<sup>84</sup> The results from RCTs are inconsistent. After 6.8 years of follow-up, the HERS II showed a nonsignificant protective effect of estrogen (RR

0.81, 95% CI 0.46–1.45) (Fig. 2),<sup>28</sup> whereas the WHI trial demonstrated a nominally significant protective effect in healthy postmenopausal women after 3 years of HRT use (RR 0.63, 95% CI 0.32–1.24) (Fig. 3).<sup>14</sup>

Data based on observational and case-control studies suggest a 1.5- to 2-fold increased risk of ovarian cancer with HRT.<sup>85–87</sup> RCTs confirming these results are lacking, as is evidence contraindicating HRT use in ovarian cancer survivors at this time.

Observational evidence on the effect of HRT on certain systemic diseases is controversial. HRT has been shown to be beneficial in some diseases, such as type 2 diabetes mellitus,<sup>88</sup> osteoarthritis<sup>89</sup> and rheumatoid arthritis,<sup>90</sup> but not in others, including systemic lupus erythematosus,<sup>91</sup> antiphospholipid antibody syndrome<sup>92</sup> and asthma.<sup>93,94</sup> Again, RCT data are lacking, although studies are under way to assess these issues further.<sup>92</sup>

### The role of androgen replacement therapy

Although HRT most frequently refers to the replacement of estrogen or progesterone, or both, the therapeutic use of androgen replacement in women is becoming more widespread, despite limited data.

Evidence suggests that androgen replacement therapy in postmenopausal women receiving HRT increases bone mineral density,<sup>95,96</sup> libido and overall well-being.<sup>97–100</sup> How-

**Table 3: HRT use in 10 000 women: benefits and harms per year\***

Benefit/harm	Relative risk (and 95% CI) from review and meta-analysis	Hazard ratio (and 95% CI) from WHI trial <sup>14</sup>	Age, yr; no. of events prevented or caused per year					
			55–64		65–74		75–84	
			Review	WHI trial	Review	WHI trial	Review	WHI trial
<b>Benefit (prevention)</b>								
Hip fracture	0.76 (0.56–1.01)	0.66 (0.33–1.33)	3	4	9	13	33	47
Wrist fracture	0.44 (0.23–0.84)	NA	34	–	37.5	–	45	–
Vertebral fracture	0.60 (0.36–0.99)	0.66 (0.32–1.34)	32	27	57	49	91	78
Colon cancer	0.80 (0.74–0.86)	0.63 (0.32–1.24)	2	3	4	7	7	12.5
<b>Uncertain benefit</b>	0.66 (0.53–0.82)	NA	17‡	–	34	–	68‡	–
<b>Harm (caused)</b>								
CAD event	0.91 (0.67–1.33)	1.29 (1.02–1.63)	0	6	0	9	0	11.5
Stroke	1.12 (1.01–1.23)	1.41 (0.86–2.31)	1‡	4‡	3	9	6‡	19‡
Thromboembolic event	2.14 (1.64–2.81)	2.11 (1.26–3.55)	1.5	1.4	1.5	1.4	1.5	1.4
Thromboembolic event during first year of use	3.49 (2.33–5.59)	NA	3	–	3	–	3	–
Breast cancer								
< 5 yr of use	1.0 to 1.14	NA	0–2.5	–	0–6	–	0–7	–
≥ 5 yr of use	1.23 to 1.35	1.26 (1.00–1.59)	7–11	8	10–15	11	11–17	12
Cholecystitis								
< 5 yr of use	1.8 (1.6–2.0)	NA	25	–	25	–	25	–
≥ 5 yr of use	2.5 (2.0–2.9)	NA	53.5	–	53.5	–	53.5	–

Note: NA = not applicable, – = data not computed.

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†Nominal CIs are indicated for main outcomes of the trial (breast cancer and CAD), adjusted CIs, for secondary outcomes.

‡Estimates are based on extrapolations.

ever, the clinical utility of androgen replacement therapy is currently limited by the lack of an approved effective androgen replacement preparation that reliably returns serum androgen levels to normal in women and that has an appropriate safety profile. Low dosages of androgen may be considered in women receiving HRT who have androgen deficiency symptoms, but it is essential that patients be aware of the adverse effects of and contraindications to androgen replacement therapy.<sup>96,98,101</sup> Widespread screening for androgen deficiency is not recommended at this time owing to the lack of established diagnostic guidelines defining androgen deficiency in women and the clinical profile of the patient most responsive to androgen replacement therapy.

## The case revisited

Ms. R presents with several issues that need to be addressed. She has osteopenia of the lumbar spine, which may increase her risk of vertebral fracture up to 2-fold,<sup>102</sup> but no history of fractures. She does not currently have known CAD but does have cardiac risk factors, including dyslipidemia, hypertension and a family history of CAD. Based on Framingham Study data, these factors predict a low 10-year risk of CAD.<sup>103</sup> In addition, having a first-degree relative with a history of breast cancer gives her a 5-year risk of breast cancer of 2%–3%.<sup>104</sup> (Breast cancer risk can be calculated using the Breast Cancer Risk Assessment Tool available online [<http://bcra.nci.nih.gov/brc/>].)

Ms. R has 2 indications for HRT to consider: estrogen-deficiency symptoms and prevention of osteoporosis. Menopausal symptoms are successfully treated with short-term HRT. However, she will require at least 5 years of HRT to see a benefit in reduction of the risk of vertebral fractures. Conversely, her risk of breast cancer would further increase by 2-fold after 10 years of HRT. Given her cardiac risk factors, she is at risk of CAD, but the WHI trial results do not support the use of HRT for primary prevention of CAD. She has no other known absolute contraindications to estrogen or progesterone use, including unexplained vaginal bleeding, active liver disease, venous thromboembolism or history of endometrial or breast cancer.

Accordingly, short-term (less than 3 years) HRT would be beneficial in decreasing her menopausal symptoms while minimally increasing her absolute risk of breast cancer, but without offering any protection against (and possibly increasing risk of) CAD and venous thromboembolism.<sup>14</sup> Alternatively, Ms. R can use nonhormonal treatments to relieve her menopausal symptoms, such as antidepressants or clonidine for her hot flashes, and lubricants or small doses of topically applied estrogen cream, with minimal systemic effects, for her vaginal dryness. Although estrogen therapy may also be helpful in lowering her low-density lipoprotein cholesterol level and increasing her high-density lipoprotein cholesterol level, studies have established the increased risk of CAD with HRT, which would therefore render HRT use counterintuitive. If her dyslipidemia progresses

despite changes in diet and physical activity, antilipid agents should be considered. Her personal risk of cardiovascular disease and breast cancer may be relatively low compared to the benefit of resolution of her symptoms in the short duration. However, short-term HRT has not been shown to affect the risk of vertebral fractures, and longer duration of HRT can increase her risk of breast cancer. Therefore, alternative nonhormonal treatments to reduce her fracture risk, including bisphosphonates and selective estrogen-receptor modulators, may be considered after she optimizes her calcium and vitamin D intake and undertakes an appropriate exercise regimen.

## Conclusion

Use of HRT should be individualized, the risks and benefits of HRT for each woman being taken into consideration. Based on the results of the WHI trial,<sup>14</sup> HRT use for 1 year in 10 000 healthy postmenopausal women is associated with 7 more CAD events, 8 more invasive breast cancers, 8 more strokes, 8 more pulmonary emboli, 6 fewer colorectal cancers and 5 fewer hip fractures (Table 3). Our role as physicians and health care providers is to clearly inform patients about both the benefits and the limitations of HRT, taking into account patients' preferences and concerns. Above all, it is important to implement proven preventive measures, including regular breast self-examination<sup>105</sup> (although controversial), clinical breast examinations, annual mammography and adequate calcium and vitamin D intake, as well as adopting an appropriate exercise regimen and a low-fat diet.

This article has been peer reviewed.

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## References

1. Greendale G, Reboussin B, Hogan P. Symptom relief and side effects of postmenopausal hormones: results from the Postmenopausal Estrogen/Progestin Interventions Trial. *Obstet Gynecol* 1998;92:982-88.
2. Cardozo L, Bachmann G, McClish D, Fonda D, Birgerson L. Meta-analysis of estrogen therapy in the management of urogenital atrophy in postmenopausal women: second report of the Hormones and Urogenital Therapy Committee. *Obstet Gynecol* 1998;92:722-7.
3. Barrett-Connor E, Grady D. Hormone replacement therapy, heart disease, and other considerations. *Annu Rev Public Health* 1998;19:55-72.
4. Grady D, Rubin S, Petitti D, Fox CS, Black D, Ettinger B, et al. Hormone therapy to prevent disease and prolong life in postmenopausal women. *Ann Intern Med* 1992;117:1016-37.
5. Stampfer M, Colditz G. Estrogen replacement therapy and coronary heart disease: a quantitative assessment of the epidemiologic evidence. *Prev Med* 1991;20:47-63.
6. Anderson H. Estrogen therapy, atherosclerosis, and clinical cardiovascular events. *Circulation* 1996;94:1809-11.
7. Mosca L. Estrogen and atherosclerosis. *J Invest Med* 1998;46:381-6.
8. Guetta V, Cannon R. Cardiovascular effects of estrogen and lipid-lowering therapies in postmenopausal women. *Circulation* 1996;93:1928-37.
9. Mendelsohn M, Karas R. The protective effects of estrogen on the cardiovascular system. *N Engl J Med* 1999;340:1801-11.



10. Hulley S, Grady D, Bush T, Furberg C, Herrington D, Riggs B, 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* 1998;280:605-13.
11. Grady D, Herrington D, Bittner V, Blumenthal R, Davidson M, Hlatky M, et al. Cardiovascular disease outcomes during 6.8 years of hormone therapy (HERS II). *JAMA* 2002;288:49-57.
12. Viscoli C, Brass L, Kernan W, Sarrel P, Suissa S, Horowitz R. A clinical trial of estrogen-replacement therapy after ischemic stroke. *N Engl J Med* 2001;345:1243-9.
13. Simon J, Hsia J, Cauley JA, Richards C, Harris F, Fong J, et al. Postmenopausal hormone therapy and risk of stroke: the Heart and Estrogen/progestin Replacement Study (HERS). *Circulation* 2001;103:638-42.
14. Writing Group for the Women's Health Initiative Investigators. Risk and benefits of estrogen plus progestin in healthy postmenopausal women. Principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002;288:321-33.
15. Clarke SC, Kelleher J, Lloyd-Jones H, Slack M, Scholfield PM. A study of hormone replacement therapy in postmenopausal women with ischaemic heart disease: the Papworth HRT atherosclerosis study. *BJOG* 2002;109:1056-62.
16. Writing Group for the PEPI Trial. Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women. The Postmenopausal Estrogen/Progestin Interventions Trial. *JAMA* 1995;273:199-208.
17. Herrington D, Reboussin D, Brosnihan B, Sharp PC, Shumaker SA, Snyder TE, et al. Effects of estrogen replacement on the progression of coronary-artery atherosclerosis. *N Engl J Med* 2000;343:522-9.
18. Hodis H, Mack W, Lobo R, Shoupe D, Sevanian A, Mahler PR, et al. Estrogen in the Prevention of Atherosclerosis. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 2001;135:939-53.
19. Waters DD, Alderman EL, Hsia J, Howard BV, Cobb FR, Rogers WJ, et al. Effects of hormone replacement therapy and antioxidant vitamin supplements on coronary atherosclerosis in postmenopausal women: a randomized controlled trial. *JAMA* 2002;288:2432-40.
20. Mosca L, Collins P, Herrington D, Mendelsohn ME, Pasternak RC, Robertson RM, et al. Hormone replacement therapy and cardiovascular disease. A statement for healthcare professionals from the American Heart Association. *Circulation* 2001;104:499-503.
21. Wells G, Tugwell P, Shea B, Guyatt G, Peterson J, Zytaruk N, et al. Meta-analyses of therapies for postmenopausal women. V. Meta-analysis of the efficacy of hormone replacement therapy in treating and preventing osteoporosis in postmenopausal women. *Endocr Rev* 2002;23(4):529-39.
22. Villareal D, Binder E, Williams D, Schechtman K, Yarasheski K, Kohrt W. Bone mineral density response to estrogen replacement in frail elderly women: a randomized controlled trial. *JAMA* 2001;286:815-20.
23. Lufkin E, Wahnner H, O'Fallon W. Treatment of postmenopausal osteoporosis with transdermal estrogen. *Ann Intern Med* 1992;117:1-9.
24. Wimalawansa S. A four-year randomized controlled trial of hormone replacement and bisphosphonate, alone or in combination, in women with postmenopausal osteoporosis. *Am J Med* 1998;104:219-26.
25. Komulainen M, Kroger H, Tuppurainen M, Heikkinen AM, Alhava E, Honkanen R, et al. HRT and vitamin D in prevention of non-vertebral fractures in postmenopausal women: a 5 year randomized trial. *Maturitas* 1998;31:45-54.
26. Mosekilde L, Beck-Nielsen H, Sorensen OH, Nielsen SP, Charles P, Vestergaard P, et al. Hormonal replacement therapy reduces forearm fracture incidence in recent postmenopausal women — results of the Danish Osteoporosis Prevention Study. *Maturitas* 2000;36:181-93.
27. Cauley J, Black D, Barrett-Connor E, Harris F, Shields K, Applegate W, et al. The effects of hormone replacement therapy on clinical fractures and height loss: the Heart and Estrogen/progestin Replacement Study. *Am J Med* 2001;110:442-50.
28. Hulley S, Furberg C, Barrett-Connor E, Cauley J, Grady D, Haskell W, et al. Noncardiovascular disease outcomes during 6.8 years of hormone therapy. HERS II. *JAMA* 2002;288:58-66.
29. Windeler J, Lange S. Events per person year: a dubious concept. *BMJ* 1995;310:454-6.
30. Torgerson D, Bell-Syer S. Hormone replacement therapy and prevention of nonvertebral fractures: a meta-analysis of randomized trials. *JAMA* 2001;285:2891-7.
31. US Food and Drug Administration. FDA approves new labels for estrogen and estrogen with progestin therapies for postmenopausal women following review of Women's Health Initiative data [press release PO3-01]. *FDA News* 2003 Jan 8. Available: [www.fda.gov/bbs/topics/NEWS/2003/NEW00863.html](http://www.fda.gov/bbs/topics/NEWS/2003/NEW00863.html) (accessed 2003 Mar 12).
32. Brown JP, Josse RG. 2002 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada. *CMAJ* 2002;167(Suppl 10):S1-34.
33. McClung M, Geusens P, Miller P, Zippel H, Benson WG, Roux C, et al. Effect of risedronate on the risk of hip fracture in elderly women. *N Engl J Med* 2001;344:333-40.
34. FIT Research Group. Fracture risk reduction with alendronate in women with osteoporosis: the Fracture Intervention Trial. *J Clin Endocrinol Metab* 2000;85:4118-24.
35. Ettinger B, Black DM, Mitlak BH, Knickerbocker RK, Nickelsen T, Genant HK, et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. *JAMA* 1999;282:637-45.
36. Chesnut CH III, Silverman S, Andriano K, Genant H, Gimona A, Harris S, et al. A randomized trial of nasal spray salmon calcitonin in postmenopausal women with established osteoporosis: the prevent recurrence of osteoporotic fractures study. PROOF Study Group. *Am J Med* 2000;109:267-76.
37. Smith CA, McCleary CA, Murdock GA, Wilshire TW, Buckwalter DK, Bretsky P, et al. Lifelong estrogen exposure and cognitive performance in elderly women. *Brain Cogn* 1999;39:203-18.
38. Zandi PP, Carlson MC, Plassman BL, Welsh-Bohmer KA, Mayer LS, Steffens DC, et al. Hormone replacement therapy and incidence of Alzheimer disease in older women: the Cache County Study. *JAMA* 2002;288:2123-9.
39. Phillips S, Sherwin B. Effects of estrogen on memory function in surgically menopausal women. *Psychoneuroendocrinology* 1992;17:485-95.
40. Sherwin BB. Estrogen and/or androgen replacement therapy and cognitive functioning in surgically menopausal women. *Psychoneuroendocrinology* 1988;13:345-57.
41. Fedor-Freybergh P. The influence of oestrogens on the wellbeing and mental performance in climacteric and postmenopausal women. *Acta Obstet Gynecol Scand Suppl* 1977;64:1-91.
42. Dittkoff E, Cray W, Cristo M, Lobo R. Estrogen improves psychological function in asymptomatic postmenopausal women. *Obstet Gynecol* 1991;78:991-5.
43. Hackman B, Galbraith D. Replacement therapy and piperazine oestrone sulphate and its effect on memory. *Curr Med Res Opin* 1976;4:303-6.
44. Caldwell B, Watson R. An evaluation of psychological effects of sex hormone administration in aged women: results after six months. *J Gerontol* 1952;7:228-44.
45. Campbell S, Whitehead M. Oestrogen therapy and the menopausal syndrome. *Clin Obstet Gynaecol* 1977;4:31-47.
46. Honjo H, Ogino Y, Naitoh K, Urabe M, Kitawaki J, Yasuda J, et al. In vivo effects by estrone sulfate on the central nervous system-senile dementia (Alzheimer's type). *J Steroid Biochem* 1989;34(1-6):521-5.
47. Fillit H, Weinreb H, Cholst I, Luine V, McEwen B, Amador R, et al. Observations in a preliminary open trial of estradiol therapy for senile dementia-Alzheimer's type. *Psychoneuroendocrinology* 1986;11:337-45.
48. Ohkura T, Isse K, Akazawa K, Hamamoto M, Yaoi Y, Hagino N, et al. Evaluation of estrogen treatment in female patients with dementia of the Alzheimer type. *Endocr J* 1994;41:361-71.
49. Honjo H, Ogino Y, Naitoh K, et al. An effect of conjugated estrogen to cognitive impairment in women with senile dementia-Alzheimer's type: a placebo-controlled double blind study. *J Jpn Menopause Soc* 1993;1:167-71.
50. Shumaker SA, Reboussin BA, Espeland MA, Rapp SR, McBeew WL, Dailey M, et al. The Women's Health Initiative Memory Study (WHIMS): a trial of the effect of estrogen therapy in preventing and slowing the progression of dementia. *Controlled Clin Trials* 1998;19:604-21.
51. Clemons M, Goss P. Mechanisms of disease: estrogen and the risk of breast cancer. *N Engl J Med* 2001;344:276-85.
52. Rosner B, Colditz G, Willett W. Reproductive risk factors in a prospective study of breast cancer: Nurses' Health Study. *Am J Epidemiol* 1994;139:819-35.
53. Colditz G, Egan K, Stampfer M. Hormone replacement therapy and risk of breast cancer. Results of epidemiologic studies. *Am J Obstet Gynecol* 1993;168:1473-80.
54. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormone replacement therapy: collaborative re-analysis of data from 51 epidemiologic studies of 52,705 women with breast cancer and 108,411 women without breast cancer. *Lancet* 1997;350:1047-59.
55. Steinberg KK, Smith SJ, Thacker SB, Stroup DF. Breast cancer risk and duration of estrogen use: the role of study design in meta-analysis. *Epidemiology* 1994;5:415-21.
56. Steinberg K, Thacker S, Smith S, Stroup DF, Zack MM, Flanders WD, et al. A meta-analysis of the effect of estrogen replacement on the risk of breast cancer. *JAMA* 1991;265:1985-90.
57. Boyd N, Byng J, Jong R, Fishell EK, Little LE, Miller AB, et al. Quantitative classification of mammographic densities and breast cancer risk: results from the Canadian National Breast Screening Study. *J Natl Cancer Inst* 1995;87:670-5.
58. Schairer C, Lubin J, Troisi R, Sturgeon S, Brinton L, Hoover R. Menopausal estrogen and estrogen-progestin replacement therapy and breast cancer risk. *JAMA* 2000;283:485-91.
59. Santen R, Pinkerton J, McCartney C, Petroni G. Clinical review: risk of breast cancer with progestins in combination with estrogen as hormone replacement therapy. *J Clin Endocrinol Metab* 2001;86:16-23.
60. Magnusson C, Baron JA, Correia N, Bergstrom R, Adami H, Persson I. Breast-cancer risk following long-term oestrogen- and oestrogen-progestin-replacement therapy. *Int J Cancer* 1999;81:339-44.
61. Ross R, Paganini-Hill A, Wan P, Pike M. Effect of hormone replacement therapy on breast cancer risk: estrogen vs estrogen plus progestin. *J Natl Cancer Inst* 2000;92:328-32.
62. Sellers T, Mink P, Cerhan J, Zheng W, Anderson KE, Kushi LH, et al. The role of hormone replacement therapy in the risk for breast cancer and total mortality in women with a family history of breast cancer. *Ann Intern Med* 1997;127:973-80.
63. Hoskins K, Stopfer J, Calzone K, Merajver SD, Rebbeck TR, Garber JE, et

al. Assessment and counseling for women with a family history of breast cancer. A guide for clinicians. *JAMA* 1995;273:577-85.

64. Vassilopoulos-Sellin R, Asmar L, Hortobagyi G, Klein MJ, McNeese M, Singletary SE, et al. Estrogen replacement therapy after localized breast cancer: clinical outcome of 319 women followed prospectively. *J Clin Oncol* 1999; 17:1482-7.

65. DiSaia P, Grosen E, Kurosaki T, Gildea M, Cowan B, Anton-Culver H. Hormone replacement therapy in breast cancer survivors: a cohort study. *Am J Obstet Gynecol* 1996;174:1494-8.

66. Cobleigh M, Berris R, Bush T, Davidson NE, Robert NJ, Sparano JA, et al. Estrogen replacement therapy in breast cancer survivors: a time for change. *JAMA* 1994;272:540-5.

67. Treatment of estrogen deficiency symptoms in women surviving breast cancer. *J Clin Endocrinol Metab* 1998;83:1993-2000.

68. Loprinzi C, Kugler J, Sloan J, Mailliard JA, LaVasseur BI, Barton DL, et al. Venlafaxine in management of hot flashes in survivors of breast cancer: a randomized controlled trial. *Lancet* 2000;356:2059-63.

69. Loprinzi CL, Barton D. Estrogen deficiency: in search of symptom control and sexuality [editorial]. *J Natl Cancer Inst* 2000;92:1028-9.

70. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994;344:1383-9.

71. Grady D, Gebretsadik T, Kerlikowske K, Ernster V, Petitti D. Hormone replacement therapy and endometrial cancer risk: a meta-analysis. *Obstet Gynecol* 1995;85:304-13.

72. Lethaby A, Farquhar C, Sarkis A, Roberts H, Jepson R, Barlow D. Hormone replacement therapy in postmenopausal women: endometrial hyperplasia and irregular bleeding [Cochrane review]. In: Cochrane Database of Systematic Reviews; 2000(2): CD000402. Oxford: Update Software.

73. Writing Group for the PEPI Trial. Effects of hormone replacement therapy on endometrial histology in postmenopausal women. The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. *JAMA* 1996;275:370-5.

74. Miller J, Chan BK, Nelson HD. Postmenopausal estrogen replacement and risk for venous thromboembolism: a systematic review and meta-analysis for the U.S. Preventive Services Task Force. *Ann Intern Med* 2002;136:680-90.

75. Nelson HD, Humphrey LL, Nygren P, Teutsch SM, Allan JD. Postmenopausal hormone replacement therapy: scientific review. *JAMA* 2002;288:872-81.

76. Perez G, Garcia R, Castellsague J, Duque O. Hormone replacement therapy and risk of venous thromboembolism: population based case-control study. *BMJ* 1997;314:796-800.

77. Hoibraaten E, Qvigstad E, Arnesen H, Larsen S, Wickstrom E, Sandset P. Increased risk of recurrent venous thromboembolism during hormone replacement therapy — results of the randomized, double-blind, placebo-controlled study in venous thromboembolism trial (EVTE). *Thromb Haemost* 2000;84:961-7.

78. Giltay EJ, Gooren LJ, Emeis JJ, Kooistra T, Stehouwer CD. Oral, but not transdermal, administration of estrogens lowers tissue-type plasminogen activator levels in humans without affecting endothelial synthesis. *Arterioscler Thromb Vasc Biol* 2000;20:1396-403.

79. Scarabin P, Alhenc-Gelas M, Plu-Bureau G, Taisne P, Agher R, Aiach M. Effects of oral and transdermal estrogen/progesterone regimens on blood coagulation and fibrinolysis in postmenopausal women: a randomized controlled trial. *Arterioscler Thromb Vasc Biol* 1997;17:3071-8.

80. North American Menopause Society. A decision tree for the use of estrogen replacement therapy or hormone replacement therapy in postmenopausal women: consensus opinion of the North American Menopause Society. *Menopause* 2000;7:76-86.

81. Creinin M, Lisman R, Strickler R. Screening for factor V Leiden mutation before prescribing combination oral contraceptives. *Fertil Steril* 1999;72:646-51.

82. Grodstein F, Colditz G, Stampfer M. Postmenopausal hormone use and cholecystectomy in a large prospective study. *Obstet Gynecol* 1994;83:5-11.

83. Nanda K, Bastian L, Hasselblad V. Hormone replacement and the risk of colorectal cancer: a meta-analysis. *Obstet Gynecol* 1999;93:880-8.

84. Crandall CJ. Estrogen replacement therapy and colon cancer: a clinical review. *J Womens Health Genet Based Med* 1999;9:1155-66.

85. Rodriguez C, Patel A, Calle E, Jacob E, Thun M. Estrogen replacement therapy and ovarian cancer mortality in a large prospective study of US women. *JAMA* 2001;285:1460-5.

86. Bosze P, Bast R, Berchuck A, Burke HB, Buller RE, Creasman WT, et al. Consensus statements on prognostic factors in epithelial ovarian carcinoma. Report of the Consensus Meeting organized by the European Society of Gynaecological Oncology, ESGO. *Eur J Gynaecol Oncol* 2000;21:513-26.

87. Whittemore A, Harris R, Itnyre J. Characteristics relating to ovarian cancer risk: collaborative analysis of 12 US case-control studies. II. Invasive epithelial ovarian cancers in white women. Collaborative Ovarian Cancer Group. *Am J Epidemiol* 1992;136:1184-203.

88. Friday K, Dong C, Fontenot R. Conjugated equine estrogen improves glycemic control and blood lipoproteins in postmenopausal women with type II diabetes. *J Clin Endocrinol Metab* 2001;86:48-52.

89. Nevitt M, Felson D. Sex hormones and the risk of osteoarthritis in women: epidemiological evidence. *Ann Rheum Dis* 1996;55:673-6.

90. MacDonald AG, Murphy EA, Capell HA, Bankowska UZ, Ralston SH. Effects of hormone replacement therapy in rheumatoid arthritis: a double blind placebo-controlled study. *Ann Rheum Dis* 1994;53:54-7.

91. Sanchez-Guerrero J, Liang MH, Karlson EW, Hunter DJ, Colditz GA. Postmenopausal estrogen therapy and the risk for developing systemic lupus erythematosus. *Ann Intern Med* 1995;122:430-3.

92. Buyon JP. Hormone replacement therapy in postmenopausal women with systemic lupus erythematosus. *J Am Med Womens Assoc* 1998;53:13-7.

93. Lieberman D, Kopernik G, Porath A, Lazer S, Heimer D. Subclinical worsening of bronchial asthma during estrogen replacement therapy in asthmatic postmenopausal women. *Maturitas* 1995;21:153-7.

94. Troisi RJ, Speizer FE, Willett WC, Trichopoulos D, Rosner B. Menopause, postmenopausal estrogen preparations, and the risk of adult-onset asthma. A prospective cohort study. *Am J Respir Crit Care Med* 1995;152(4 Pt 1):1183-8.

95. Barrett-Connor E, Young R, Notelovitz M, Sullivan J, Wiita B, Yang HM, et al. A two-year, double-blind comparison of estrogen-androgen and conjugated estrogens in surgically menopausal women. Effects on bone mineral density, symptoms and lipid profiles. *J Reprod Med* 1999;44:1012-20.

96. Davis S. Androgen replacement in women: a commentary. *J Clin Endocrinol Metab* 1999;84:1886-91.

97. Basson R, Berman J, Burnett A, Derogatis L, Ferguson D, Fourcroy J, et al. Report of the international consensus development conference on female sexual dysfunction: definitions and classifications. *J Urol* 2000;163:888-93.

98. Arlt W, Callies F, van Vlijmen J, Koehler I, Reincke M, Bidlingmaier M, et al. Dehydroepiandrosterone replacement in women with adrenal insufficiency. *N Engl J Med* 1999;341:1013-20.

99. Davis S, McCloud P, Strauss B, Burger H. Testosterone enhances estradiol's effects on postmenopausal bone density and sexuality. *Maturitas* 1995;21:227-36.

100. Shifren J, Braunstein G, Simon J, Casson PR, Buster JE, Redmond GP, et al. Transdermal testosterone treatment in women with impaired sexual function after oophorectomy. *N Engl J Med* 2000;343:682-8.

101. Hickok L, Toomey C, Speroff L. A comparison of estrified estrogens with and without methyltestosterone: effects on endometrial histology and serum lipoproteins in postmenopausal women. *Obstet Gynecol* 1993;82:919-24.

102. Siris E, Miller P, Barrett-Connor E, Faulkner KG, Wehren LE, Abbott TA, et al. Identification and fracture outcomes of undiagnosed low bone mineral density in postmenopausal women: results from the National Osteoporosis Risk Assessment. *JAMA* 2001;286:2815-22.

103. Wilson P, D'Agostino R, Levy D, Belanger A, Silbershatz H, Kannel W. Prediction of coronary heart disease using risk factor categories. *Circulation* 1998; 97:1837-47.

104. Gail M, Brinton L, Byar D, Corle DK, Green SB, Schairer C, et al. Projecting individualized probabilities of developing breast cancer for white females who are being examined annually. *J Natl Cancer Inst* 1989;81:1879-86.

105. Nekhlyudov L, Fletcher S. Is it time to stop teaching breast self-examination? [editorial] *CMAJ* 2002;164(13):1851-2.

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**Appendix 1: Literature search strategy**

We conducted a literature search of MEDLINE (1966–2001) and the Cochrane Controlled Trials Register (www.cochranelibrary.com), using the search words “postmenopausal,” “perimenopausal,” “hormone replacement therapy,” “estrogen,” “progesterin” and “progesterone” to identify English-language articles about the association of use of hormone replacement therapy for the following topics:

- Cardiovascular disease, myocardial infarction, angina, stroke, lipids
- Bone density, osteoporosis, fractures
- Thromboembolism
- Breast cancer
- Cognition, dementia, Alzheimer's disease
- Endometrial cancer, ovarian cancer, colon cancer
- Gallbladder disease
- Diabetes mellitus, systemic lupus erythematosus, arthritis
- Androgen replacement therapy, testosterone

We obtained additional articles by reviewing the bibliography of each of the retrieved articles along with other reviews and editorials. Only published data were reviewed in the paper. The literature search focused primarily on recent evidence in this field (from 1990 to 2001), with reference to several key studies that were completed before this time. We critically appraised the articles for appropriateness of data contribution to the paper.