The benefits of oestrogen following menopause: why hormone replacement therapy should be offered to postmenopausal women

Barry G Wren

ABSTRACT

- Recently, two major epidemiological studies found that hormone replacement therapy (HRT) in postmenopausal women increased the risk of breast cancer. One of the studies also found that HRT increased the risk of cardiovascular disease and thrombosis. As a consequence, women were advised to cease this therapy.
- However, detailed analysis of these studies suggests that the conclusions may be erroneous. Other studies suggest that the timing of initiation of HRT for healthy women is critical to achieving a beneficial outcome.
- When begun within 5 years of menopause in healthy women, oestrogen-based HRT results in far greater benefits than adverse outcomes.
- There is substantial objective evidence that the benefits of HRT include:
  - Reduced distressing symptoms of menopause.
  - Reduced risk of osteoporotic fractures, dementia and colorectal cancer.
  - Improved wellbeing, quality of life; improved vaginal epithelium, sexual enjoyment and bladder capacity.
  - Improved cardiovascular system, with reduced myocardial ischaemia and cardiovascular-related death.
  - Increased longevity.
- The adverse effects of HRT include:
  - Oral HRT doubles the risk of thromboembolism.
  - HRT promotes growth of pre-existing breast cancer.

MJA 2009; 190: 321–325

For over 70 years, women have used oestrogen-based hormone replacement therapy (HRT) to relieve distressing symptoms associated with menopause.[1,2] In that period, a number of cohort and case–control studies demonstrated that HRT was associated with a reduction in cardiovascular disease,[3,4] osteoporosis[5,6] and dementia;[7,8] other studies reported improvements in general wellbeing and sexual enjoyment.[2,9]

Doubt over the long-term safety of HRT led to the Women's Health Initiative (WHI), a large, prospective, double-blind, placebo-controlled trial that used equine oestrogen (Premarin, Wyeth) and medroxyprogesterone acetate (Provera, Pfizer). The WHI was initiated under the auspices of the National Institutes of Health in the United States, and the results were published in 2002.[10] Following wide media reporting and publicity, this study had a dramatic negative effect on the prescribing habits and recommendations for health professionals. Subsequently, a number of supplementary reports were published that provided detailed information on individual health issues,[11-14] and which have resulted in diverging opinions regarding certain aspects of the WHI study.

Another study conducted by the WHI Investigators examined the effect of equine oestrogen alone on the health of postmenopausal women who had undergone hysterectomy, and was published in 2004.[15]

In the United Kingdom, a large cohort study, the Million Women Study (MWS) was published in 2003.[16] It also received wide media exposure because it found that HRT increased the risk of breast cancer in trial participants.

The initial WHI study and the MWS found that oestrogen-based HRT increased women's risk of breast cancer; the WHI study also reported that HRT increased the risk of myocardial infarction, stroke and dementia.[10,11,16] Because of these negative findings, many health professionals stopped prescribing oestrogen-based hormonal therapy, and women were bewildered by the conflicting information regarding the safety of HRT.[17]

I briefly review these seminal studies to clarify why they have produced such conflicting results.

The Women's Health Initiative

Oestrogen plus progestogen[10]

The initial WHI study recruited 16 608 postmenopausal women (exclusion criteria were hot flushes and a history of cancer), who received either Premarin plus Provera or a placebo. Although the study was intended to last for 8.5 years, it was terminated early (at 5.2 years) because of a non-significant increase in the incidence of breast cancer (38/10 000/year in the trial group v 30/10 000/year in the placebo group) and a statistically significant increase in myocardial infarction (37 v 30/10 000/year), thromboembolism (34 v 16/10 000/year) and stroke (29 v 21/10 000/year). There was also a statistically significant reduction in hip fractures (10 v 15/10 000/year) and in colorectal cancer (10 v 16/10 000/year).

A criticism of the WHI study is that two-thirds of the participants were over 60 years of age at recruitment (an average age of 63.3 years — 12–15 years after menopause); 34% were obese and a further 35% were overweight; 50% were past or current smokers; 35.7% were being treated for hypertension; 12.5% had elevated cholesterol levels; and 4.4% had diabetes. These older women are not typical of women seeking hormonal therapy as they enter menopause.[18] During the trial, 42% of women on HRT had their treatment disclosed because of symptoms, increasing the potential for bias in the statistical review; and 10.7% of women on placebo initiated their own form of hormonal therapy,[10] further complicating the trial's conclusions.

These factors could have increased the risk of cardiovascular events in older women while using oral oestrogen, which passes directly to the liver and is known to increase the risk of thrombosis in women with damaged vascular endothelium.[19] However, in spite of these problems, there was no increase in overall mortality among women taking HRT.[10]

1 Risk of medical events in the WHI studies

	Breast cancer	MI	VTE	Stroke	Hip fracture	Colorectal cancer
WHI (Premarin + Provera)[10]	+ 26%	+ 29%	+ 113%	+ 41%	–34%	–37%
WHI (Premarin alone)[15]	–23%	–8%	+34%	+ 39%	–39%	+ 8%

WHI = Women's Health Initiative. MI = myocardial infarction. VTE = venous thromboembolism. ◆

Oestrogen only[15]

In 2004, the WHI research group published another article of considerable significance.[15] This study included 10 739 postmenopausal women with prior hysterectomy, who received either unopposed oral Premarin only or a placebo. After 6.8 years, it was found that women receiving oestrogen (without a progestogen) had a 23% reduction in the incidence of breast cancer (26 v 33/10 000/year), a reduction in myocardial infarction (49 v 54/10 000/year), and a 30% reduction in osteoporosis-related fractures (139 v 195/10 000/year). The risk of thrombosis (28 v 21/10 000/year) and stroke (44 v 32/10 000/year) remained.[15]

Later analysis of the original WHI data (Premarin plus Provera) showed that women who began hormonal therapy within the first 10 years after menopause had a reduced risk of myocardial infarction and no increased risk of breast cancer,[12] suggesting that the timing of HRT initiation played a significant role in mediating the disease process.

Following closure of the WHI trial in 2002, women aged 50–59 years were invited to participate in an ancillary study involving arterial integrity as measured by calcification of the coronary arteries.[14] After 7.4 years, women who continued taking oestrogen had markedly reduced calcification scores compared with women taking a placebo (83.1 v 123.1; $P = 0.02$), indicating that oestrogen begun early and continued for at least 8 years had a markedly beneficial effect on coronary vessels.[14]

Box 1 summarises the risk of medical events found in the two WHI studies.[10,15]

The Million Women Study[16]

From 1996 to 2001, all women due to have a routine mammogram in the UK were invited to enter a study to determine factors that may increase the risk of breast cancer. The results suggested that women who were taking some form of hormone therapy had an increased risk of breast cancer, whereas women who had ceased HRT 12 or more months previously had no increased risk.[16] Although this large cohort study supported the concept that HRT led to breast cancer, the study came under intense criticism from other epidemiologists and clinicians, because data collection and interpretation were considered to be misguided.[20,21]

Major criticisms were: just over 50% of invited women eventually had a mammogram, suggesting there could have been self-selection bias in the study population; the number of women in the UK using HRT were over-represented in the study (32% v 19%); the average time from beginning therapy to diagnosis of cancer was brief (1.2 years), suggesting to clinicians that, in many cases, cancer had been present before initiating treatment and that hormones had accelerated its growth, rather than causing it; the study's failure to take into account that a sizeable number of women switched treatments during the follow-up period — some ceased therapy (22%), others resumed their HRT (19%) and 11% appeared to initiate HRT during the study period.[22]

Hormone cessation and a reduction in breast cancer

The number of women diagnosed with breast cancer in the US fell by between 6% and 8% from 2000 to 2004.[23,24] It has been suggested that the fall was due to a 40% reduction in the use of HRT following publication of the WHI studies and the MWS,[25-31] and it was claimed that this was further proof that hormones increased the risk of breast cancer.

Clinical experience,[32-36] however, suggests that the mutations that result in breast cancer[37,38] begin to accumulate during the premenopausal years[39-43] and having developed in a cell, persist in that cell until mutations in immunoglobulins, and other adhesion proteins allow invasive cancer to occur, sometimes many years later. Hormones promote rapid growth of a pre-existing breast disease. If hormones were responsible for promoting breast cancer, the first evidence of a reduction in breast cancer incidence would not be detected for at least 1–2 years after women had ceased hormone therapy. However, the reduction in breast cancer incidence in the US was observed before, or coinciding with, the publication of the WHI reports in 2002.[23,24] In Europe, there was also a sharp reduction in the use of HRT, but no accompanying fall in the detection of breast cancer.[44] More recently, Chlebowski and colleagues reported the results of a review of the incidence of breast cancer 3 years after the WHI study was completed.[45] Within 2 years of ceasing Premarin and Provera the increased incidence of breast cancer, evident in the initial WHI study, had reverted to that in the placebo group and it was suggested that this confirms that HRT was responsible for the increase in detected breast cancer. The results unfortunately do not clarify whether HRT caused or promoted breast cancer. The short interval between stopping HRT and an alteration in the number of cancers being reported suggests that hormones were promoters, not initiators, of breast cancer. A likely explanation is that the increase detected 2 years after starting HRT was due to accelerated growth of cancer in-situ and microinvasive cancers. Ceasing HRT would remove the stimulus for growth of these pre-existing cancers and result in a temporary reduction in the detection of tumours.[46] Another possible cause for the drop in diagnosed cancers is the reported reduction in the use of screening mammography over the years from 1998.[30,31]

Box 2 summarises the findings of the WHI studies and the MWS.

2 Conclusions from the Women's Health Initiative studies[10,15] and the Million Women Study[16]

Hormone replacement therapy after menopause:

- may accelerate pre-existing breast cancer growth
- increases the risk of thrombosis and stroke
- may increase the risk of myocardial ischaemia
- reduces the risk of fractures.

Oestrogen alone (Premarin):

- reduces the risk of breast cancer
- increases the risk of thrombosis and stroke
- has no influence on the risk of myocardial ischaemia
- reduces the risk of fractures. ◆

When does breast cancer begin?

According to the Australian Bureau of Statistics (ABS), breast cancer accounted for 4% of female deaths in Australia in 2006,[47] and clinical reports from the Australian Institute of Health and Welfare confirm that almost 25% of breast cancers occur in women under the age of 54 years.[48] Evidence that the changes resulting in breast cancer begin in young women has been confirmed by reports from a number of post-mortem studies on women who have died from non-malignant causes.[39-43] These autopsy studies found that at least 20%–30% of premenopausal women, including some adolescents, have already developed a large reservoir of duct cell hyperplasia or cancer in situ. In a study of breast tissue retrieved during medicolegal autopsies, researchers found that cancer in situ was present in 37% of women aged 40–54 years, and undiagnosed invasive cancer was present in 2%.[43]

At least 90 aberrant genetic mutations are implicated in breast cancer.[37,38] It is now accepted that most mutations are either inherited or occur spontaneously during mitosis.[32] Based on epidemiological studies, there are claims that HRT is a mutagen that leads to breast cancer. A complex hypothesis has been proposed, which states that oestradiol is converted by specific enzymes into catechol oestradiol, which, through further biochemical metabolism to quinone intermediates, is asserted to be a weak mutagen.[49] Synthetic progestogens have also been blamed, based on epidemiological evidence reporting an increased incidence of detected invasive breast cancers when combined oestrogen and progestogens have been used,[26] but there is no biological evidence to support either oestradiol or progestogens as a mutagen that leads to breast cancer.

Large cohort studies, observing the outcomes of women who have had diagnostic breast biopsies performed, confirm that, over periods ranging from 8–17 years, cancer developed twice as frequently in women with simple duct hyperplasia and about six times more often among women with atypical hyperplasia;[33-35] over the same period, invasive cancer occurred in 10%–15% of women with a history of cancer in situ.[33-36] These studies confirm that cell changes proceed from hyperplasia and atypical hyperplasia through cancer in situ to invasive cancer as cells accumulate genetic mutations, and that these mutations begin years before invasive cancer is diagnosed. Following menopause, HRT accelerates the growth of an already existent lesion. Ceasing HRT removes the accelerant, thereby reducing the number of cases likely to be diagnosed during a particular period. Appreciating the time sequence and the biological and clinical events underlying the development of cancer[32,37] helps us understand the apparent conflicts that currently exist between epidemiologists and clinicians regarding hormones and breast cancer.

Hormones and the cardiovascular system

According to the ABS, in 2006, 17% of registered female deaths were attributable to ischaemic heart disease and 8.6% to stroke.[47] Women have a major cardiovascular advantage over men of the same age until about 10 years after menopause, when the risk of cardiovascular disease begins to equal that of men.[1] This protection for women up to the age of 60 years is thought to be due to the residual beneficial effect of premenopausal oestrogen on the arterial and cardiac endothelium and musculature.[13,14]

Although the WHI study suggested an adverse effect of HRT on the cardiovascular system, it is likely that the time at which hormone therapy is initiated plays a significant role in the development of cardiovascular disease. A study in macaque monkeys found that if oestrogen therapy is delayed for more than 2 years, its protective effect is lost.[50] Extrapolating these results to humans suggests that HRT should be initiated within 6 years of menopause (the "window of opportunity").[50] Clinical studies in humans support these animal study results.[15,51,52] When HRT is initiated within a few years of menopause, women continue to experience a 40%–60% reduced risk of myocardial ischaemia and hypertension,[12,13,53-55] but 2–3 times increased risk of thromboembolism, to 8/10 000/year.[10,15,19]

Hormones and dementia

According to the ABS, dementia was responsible for about 5% of postmenopausal mortality in Australia in 2006.[47]

US researchers examined the effect of HRT on cognitive functioning and the incidence of dementia in 7479 women from the WHI study group.[11] The women were all aged over 65 years when they entered the study, and were followed up for 4–5 years.[11] The results from this research indicated that HRT provided no advantage in protection from dementia, and may have increased the number of women who developed dementia.[11] As a result, it was recommended that hormonal therapy should not be used to prevent or treat dementia in women.

However, to prevent or reduce the impact of a disease, it is important to begin prophylactic therapy before the onset of the disease — certainly before the age of 65 years. Research has demonstrated that β-amyloid deposition is reduced in castrated animals fed an oestrogenic therapy regimen,[56] and clinical studies have shown that women who begin oestrogen therapy at or soon after menopause have a reduced risk of dementia.[57]

Hormones and osteoporosis

Oestrogen suppresses osteoclastic activity, stimulates osteoblasts, and maintains the essential coupling between bone formation and bone resorption. Women who begin and continue HRT have a much reduced risk of osteoporotic fractures.[10,17] Studies have consistently demonstrated that women who begin HRT within the window of opportunity have a 30%–50% reduction in the risk of fracture of spine or hip.[5,10,17]

Hormones and longevity

Because of the fear of adverse events, a number of authorities have recommended that HRT be used for the shortest possible period.[58,59] However, a 22-year study of 8801 women showed that those using HRT from menopause, and continuing for the remainder of their lives, lived longer with fewer adverse events than women who did not use HRT.[51] The reduction in the risk of death from all causes was 15%. Similar studies have confirmed that women who begin HRT at or within a few years of menopause have fewer cardiovascular events or breast cancers, and live longer than similar women who never use HRT.[42,60]

Hormones and quality of life

HRT was introduced in the early 1930s to relieve hot flushes, sweats, insomnia, dry vagina and to improve the quality of life for menopausal women. Over the past 70 years, it has continued to be

the most effective therapy to reduce these symptoms. Recent studies also confirm that HRT is still the therapy of choice to maintain health, wellbeing and sexual enjoyment;[61] negative reports of increased adverse events must be balanced against the benefits of starting HRT early and continuing therapy.

In summary, HRT initiated in healthy women during the first 5 years following the menopause is responsible for:

- abating menopausal symptoms;
- improving quality of life;
- maintaining the cardiovascular system;
- reducing osteoporosis-related fractures;
- reducing the risk of dementia; and
- increasing longevity.

Adverse effects include an increase in thrombosis and stroke when HRT is administered orally to women who have an underlying cardiovascular disease, and HRT makes pre-existing breast cancer grow more rapidly.

The benefits of HRT, if initiated early enough in healthy women, are far greater than the potential adverse effects.

Competing interests

None identified.

Author details

Barry G Wren, MD, FRANZCOG, FRCOG, Director and Gynaecologist
Menopause Clinic, Sydney, NSW.
Correspondence: barrygwren@bigpond.com

References

1 Wilson RA. Feminine forever. London: WW Allen, 1966.
2 Wren BG. Oestrogen replacement therapy: the management of an endocrine deficiency disease. *Med J Aust* 1985; 142: S1-S15.
3 Stampfer MJ, Colditz GA. Estrogen replacement therapy and coronary heart disease: a quantitative assessment of the epidemiological evidence. *Prev Med* 1991; 20: 47-63.
4 Mosca L. The role of hormone replacement therapy in the prevention of postmenopausal heart disease. *Arch Intern Med* 2000; 160: 2263-2272.
5 Lindsay R, Hart DM, Aitken JM, et al. Long term prevention of post menopausal osteoporosis by oestrogen: evidence for an increased bone mass after delayed onset of oestrogen treatment. *Lancet* 1976; 1: 1038-1041.
6 Ettinger B, Gennant HK, Cann CE. Postmenopausal bone loss is prevented by treatment with low-dosage estrogen with calcium. *Ann Intern Med* 1987; 106: 40-45.
7 Tang MX, Jacobs D, Stem Y, et al. The effects of oestrogen during menopause on risk and age of onset of Alzheimer's disease. *Lancet* 1996; 348: 429-432.
8 Yaffe K, Sawaya G, Lieberburg I, Grady D. Estrogen therapy in postmenopausal women: effects on cognitive function and dementia. *JAMA* 1998; 279: 688-695.
9 Fedor-Freyberg P. The influence of oestrogen on the well-being and mental performance in climacteric and post menopausal women. *Acta Obstet Gynecol Scand* 1977; 64: 5-69.
10 Rossouw JE, Anderson GL, Prentice RL, et al; Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women. *JAMA* 2002; 288: 321-333.
11 Shumaker SA, Legault C, Rapp SR, et al; WHIMS Investigators. Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial. *JAMA* 2003; 289: 2651-2662.
12 Hsia J, Langer RD, Manson JE. Conjugated equine estrogens and coronary heart disease. The Women's Health Initiative. *Arch Intern Med* 2006; 166: 357-365.
13 Rossouw JE, Prentice RL, Manson JE, et al. Postmenopausal hormone therapy and the risk of cardiovascular disease by age and years since menopause. *JAMA* 2007; 297: 1465-1477.
14 Manson JE, Matthew AA, Rossouw JE, et al. Estrogen therapy and coronary-artery calcification. *N Engl J Med* 2007; 356: 2591-2601.
15 Writing Group for the Women's Health Initiative Study. The effects of conjugated equine estrogen in postmenopausal women with hysterectomy. *JAMA* 2004; 291: 1701-1712.
16 Beral V; Million Women Study Collaborators. Breast cancer and hormone replacement therapy in the Million Women Study. *Lancet* 2003; 362: 419-427.
17 Hersh AL, Stefanick ML, Stafford RS, et al. National use of postmenopausal hormone therapy:annual trends and response to recent evidence. *JAMA* 2004; 291: 47-53.
18 Pines A, Sturdee DW, MacLennan AH, et al. The heart of the WHI study: time for hormone therapy policies to be revised [editorial]. *Climacteric* 2007; 10: 267-269.
19 Canonico M, Plu-Bureau G, Lowe GDO, Scarabin P-Y. Hormone replacement therapy and risk of venous thromboembolism in postmenopausal women: a systematic review and meta-analysis. *BMJ* 2008; 336: 1227-1231.
20 Speroff L. The Million Women Study and breast cancer. *Maturitas* 2003; 46: 1-6.
21 Farmer R. The Million Women Study — is it believable? *Climacteric* 2005; 8: 210-213.
22 Shapiro S. The Million Women Study: potential biases do not allow uncritical acceptance of the data [editorial]. *Climacteric* 2004; 7: 3-7.
23 Jemal A, Ward E, Thun M. Recent trends in breast cancer incidence rates by age and tumor characteristics among US women. *Breast Cancer Res* 2007; 9: 108.
24 Glass AG, Lacey JV, Carreon D, Hoover RN. Breast cancer incidence, 1980–2006: combined roles of menopausal hormone therapy, screening mammography, and estrogen status. *J Natl Cancer Inst* 2007; 99: 1152-1161.
25 Canfell K, Banks E, Moa AM, Beral V. Decrease in breast cancer incidence following a rapid fall in use of hormone replacement therapy in Australia. *Med J Aust* 2008; 188: 641-644.
26 Colditz GA. Decline in breast cancer incidence due to removal of promoter: combination estrogen plus progestin. *Breast Cancer Res* 2007; 9: 108-112.
27 Chen WY, Colditz GA, Rosner B, et al. Unopposed estrogen therapy and the risk of breast cancer. *Arch Intern Med* 2006; 166: 1027-1032.
28 Clarke CA, Glasser SL, Uratsu CS, et al. Recent declines in hormone therapy utilization and breast cancer incidence: clinical and population based evidence. *J Clin Oncol* 2006; 24: e49-e50.
29 Ravdin PM, Cronin KA, Howlader N, et al. The decrease in breast cancer incidence in 2003 in the United States. *N Engl J Med* 2007; 356: 1670-1674.
30 Kerlikowske K, Miglioretti DL, Buist DSM, et al. Declines in invasive breast cancer and use of postmenopausal hormone therapy in a screening mammography population. *J Natl Cancer Inst* 2007; 99: 1335-1339.
31 Greiser CM, Greiser EM, Doren M. Menopausal hormone therapy and risk of breast cancer: a meta-analysis of epidemiological studies and randomized controlled trials. *Hum Reprod Update* 2005; 11: 561-573.
32 Wren BG. The origin of breast cancer. *Menopause* 2007; 14: 1060-1068.
33 Dupont WD, Page DL. Risk factors for breast cancer in women with proliferative breast disease. *N Engl J Med* 1985; 312: 146-151.
34 Carter CL, Corle DK, Micozzi MS, et al. A prospective study of the development of breast cancer in 16,692 women with benign breast disease. *Am J Epidemiol* 1988; 128: 467-477.
35 Tavassoli FA, Norris HJ. A comparison of the results of long-term follow up for atypical intraduct hyperplasia and intraduct hyperplasia of the breast. *Cancer* 1990; 65: 518-529.
36 Hartman LC, Sellers TA, Frost MH, et al. Benign breast disease and the risk of breast cancer. *N Engl J Med* 2005; 353: 229-237.
37 Sjöblom T, Jones S, Wood LD, et al. The consensus coding sequence of human breast and colorectal cancers. *Science* 2006; 314: 268-274.
38 Hanahan D, Weinberg R. The hallmarks of cancer. *Cell* 2000; 100: 57-70.
39 Welch HG, Black WC. Using autopsy series to estimate the disease reservoir for ductal carcinoma in situ of the breast. *Ann Intern Med* 1997; 127: 1023-1028.
40 Bartow SA, Pathak DR, Black WC, et al. Prevalence of benign, atypical and malignant breast lesions in populations at different risk for breast cancer. *Cancer* 1987; 60: 2751-2760.

41 Bhathal PS, Brown RW, Lesueur GC, Russell IS. Frequency of benign and malignant breast lesions in 207 consecutive autopsies in Australian women. *Br J Cancer* 1985; 51: 271-278.
42 Alpers CE, Wellings SR. The prevalence of carcinoma in situ in normal and cancer-associated breasts. *Hum Pathol* 1985; 16: 796-807.
43 Nielsen M, Thomsen JL, Primdahl S, et al. Breast cancer and atypia among young and middle aged women: a study of 110 medico-legal studies. *Br J Cancer* 1987; 56: 814-819.
44 Ponti A, Rosso S, Zanetti R, et al. Breast cancer incidence 1980–2006. *J Nat Cancer Inst* 2007; 99: 1817-1818.
45 Chlebowski RT, Kuller LH, Prentice RL, et al; WHI Investigators. Breast cancer after use of estrogen plus progestin in postmenopausal women. *N Engl J Med* 2009; 360: 573-587.
46 Kopans DB, Rafferty E, Georgian-Smith D, et al. A simple model of breast carcinoma growth may provide explanations for observations of apparently complex phenomena. *Cancer* 2003; 97: 2951-2959.
47 Australian Bureau of Statistics. Causes of death, Australia, 2006. Canberra: ABS, 2008. (ABS Cat. No. 3303.0.)
48 Australian Institute of Health and Welfare and National Breast Cancer Centre. Breast cancer in Australia: an overview, 2006. Canberra: AIHW, 2006. (Cancer Series No. 34. AIHW Cat. No. CAN 29.)
49 Liehr JG. Is estradiol a genotoxic mutagenic carcinogen? *Endocr Rev* 2000; 21: 40-54.
50 Clarkson T, Appt S. Controversies about HRT — lessons from monkey models. *Maturitas* 2005; 51: 64-74.
51 Paganini-Hill A, Corrada MM, Kawas CH. Increased longevity in older users of postmenopausal estrogen therapy: the Leisure World Study. *Menopause* 2006; 13: 12-18.
52 Grodstein D, Manson JE, Colditz GA, et al. A prospective, observational study of postmenopausal hormone therapy and primary prevention of cardiovascular disease. *Ann Intern Med* 2000; 133: 933-941.
53 Pines A, Sturdee DW, Birkhauser MH. Hormone therapy and cardiovascular disease in the early postmenopause: the WHI data revisited. *Climacteric* 2007; 10: 195-196.
54 Shapiro S. Risk of cardiovascular disease in relation to the use of combined postmenopausal hormone therapy: detection bias and resolution of discrepant findings in two Women's Health Initiative studies. *Climacteric* 2006; 9: 416-420.
55 Lobo RA. Postmenopausal hormones and coronary artery disease: potential benefits and risks. *Climacteric* 2007; 10 Suppl 2: 21-26.
56 Thomas T, Rhodin J. Vascular actions of estrogen and Alzheimer's disease. *Ann N Y Acad Sci* 2000; 903: 501-509.
57 Bluming AZ. Hormone replacement therapy: the debate should continue. *Geriatrics* 2004; 59: 30-37.
58 Grady D. Postmenopausal hormones — therapy for symptoms only. *N Engl J Med* 2003; 348: 1835-1837.
59 Hulley SB, Grady D. The WHI estrogen-alone trial — do things look any better? *JAMA* 2004; 291: 1769-1771.
60 Lando JF, Heck KE, Brett KM. Hormone replacement therapy and breast cancer risk in a nationally representative cohort. *Am J Prev Med* 1999; 17: 176-180.
61 Welton AJ, Vickers MR, Kim J. et al. Health related quality of life after combined hormone replacement therapy: randomized controlled trial. *BMJ* 2008; 337: a1190.

(Received 17 Jul 2008, accepted 28 Sep 2008) ❑