

## 4 SUMMARY

### HRT

#### BENEFITS FOR THE RELIEF OF MENOPAUSAL SYMPTOMS

The available evidence clearly supports the efficacy of HRT for the treatment of vasomotor symptoms in postmenopausal women. The benefits appear to be present across the Australian-approved dose regimens of both combined oestrogen/progestogen therapy and oestrogen only therapy (with the exception of nasal preparations of 100 µg oestradiol).

In general, HRT appears to have a beneficial effect upon urogenital symptoms and sexual dysfunction associated with menopause. On the basis of the available evidence, vaginal preparations appear to be as effective as oral HRT in the alleviation of vaginal symptoms.

The use of HRT appears to improve sleep, but it is not possible to determine if this improvement is independent of the alleviation of vasomotor and urogenital symptoms.

The impact of HRT upon psychological wellbeing and general quality of life is less clear, but it is important to note that baseline results for these outcomes largely fall within the age-specific normal range.

#### UNWANTED SIDE EFFECTS

There is level I and II evidence to indicate increased irregular bleeding with oral HRT compared with placebo. This was the case for both oestrogen-only and oestrogen plus progestogen, particularly when the latter was continuous. Increased bleeding also occurs with oestrogen-only transdermal administration, other than with a low dose (25 µg). No transdermal oestrogen plus progestogen studies of bleeding were available at the time of the review.

When considering the level I and II evidence on balance, it is apparent that there is no effect of HRT on weight gain.

HRT results in an increased likelihood of breast tenderness but no increase in fluid retention or migraine/headache.

#### OTHER HEALTH BENEFITS

##### *Colorectal cancer*

Currently available evidence is ambiguous with respect to the effect of HRT use upon colorectal cancer. Whilst evidence from observational studies suggests a risk reduction for both colon and rectal cancer incidence, this benefit was not statistically confirmed in the two recent large randomised controlled trials. However, both of these RCTs were conducted in an older patient population (~25% of the women had used HRT prior to baseline in the two studies). On balance, a tendency toward a decreased risk is apparent. There is insufficient information to determine differential effects of type, duration or recency of therapy on colorectal cancer risk.

### ***Osteoporotic fracture***

Good quality level I and level III-2 evidence suggests a reduced risk of fracture with HRT. Specifically, the observational evidence indicates a reduced risk that is consistent across anatomical locations. Whilst the evidence suggests that treatments with progestogen confer a greater protection, a direct comparison may not be appropriate due to the different populations of women involved. The only study (level III-2 evidence) to report fracture risk by duration of HRT use, found a benefit in > 2 years of use only.

Data from recent large RCTs (level II evidence) comparing combined HRT with placebo is inconsistent. The WHI study showed a significant reduction in 'other osteoporotic fractures' but the results for hip and vertebral fracture failed to reach statistical significance when fully adjusted. However, a more recent updated analysis of this trial suggested that HRT conferred a benefit in reducing hip, vertebral and peripheral fractures. This result is in contrast to the HERS study which showed no protective effect against fractures at any location.

Any protective benefit that is present appears to be conditional upon continued use. Evidence from past-users, shows that risk reduction is not maintained beyond 5 years after cessation of HRT.

Low potency oral and vaginal HRT appear not to offer a protective effect.

### ***Cognition/dementia***

#### **Women in general**

Interpretation of the evidence related to the effect of HRT upon cognition is difficult as studies enrol different subjects and use a wide variety of tests to measure cognitive outcomes. On balance, the evidence from existing systematic reviews and subsequent original studies fails to show a consistent benefit of HRT upon cognition. Nevertheless, there are certainly isolated studies that show a positive effect in some cognitive domains. There is level III evidence which suggests no change or a decreased risk of dementia associated with use of HRT.

#### **Women with dementia**

Overall, there is a paucity of good quality evidence regarding the association between HRT and cognitive function in women with dementia. The highest quality systematic review concluded that HRT is not indicated for cognitive improvement or maintenance in women with dementia.

## **OTHER HEALTH RISKS**

### ***Breast cancer***

#### **Women without previous breast cancer**

Evidence from high quality systematic reviews, updated with recent randomised controlled trials and observational studies confirms an increased risk of breast cancer with HRT use. However, it is important to recognise that the observed effect in both RCT and observational studies relies heavily upon data from women who are older and/or who have been taking HRT for a longer duration. In contrast, there was no apparent increase in risk amongst HRT-naïve women exposed to a shorter duration of HRT use. It is not possible to precisely determine the duration of therapy after which risk is elevated, but greater than 2–5 years appears to be associated with significantly increased risk.

The currently available evidence suggests that the risk of breast cancer may diminish as time passes after the cessation of HRT use.

There is some suggestion that the magnitude of the risk increase may be more pronounced with combined oestrogen/progestogen therapy than oestrogen alone, however it is important to bear in mind the differing populations receiving the different types of HRT. This may independently influence this finding.

The magnitude of any increased risk should be considered in the context of the absolute risk of breast cancer in this population.

### **Women with previous breast cancer**

Evidence summarised in a recent systematic review indicated no increase in breast cancer recurrence with HRT use, but a reduction in breast cancer mortality. As this evidence is primarily from observational studies, healthy user bias and in particular more regular medical follow-up of the women receiving HRT, may have confounded the results. Furthermore, the evidence is primarily from women with less severe previous breast cancer and therefore it is not clear if the results are generalisable to all women with previous breast cancer.

### ***Endometrial cancer***

There is unequivocal evidence demonstrating an increased risk of endometrial cancer when oestrogen-only HRT is used by women with an intact uterus. The magnitude of the risk elevation is large, and it is closely related to the duration of oestrogen-only HRT use. Increased risk is still significantly present amongst past users of oestrogen-only HRT. Some, but not all, studies suggest that the magnitude of risk of endometrial cancer may diminish over time.

High quality evidence from RCTs shows no indication of an increased risk of endometrial cancer amongst women with an intact uterus who used a continuous combined oestrogen/progestogen preparation. However, evidence from observational studies is less consistent, with some case-control studies reporting an elevation in risk of endometrial cancer with longer duration combined oestrogen/progestogen HRT. Nevertheless, any elevation in risk of endometrial cancer that may be present with oestrogen/progestogen combined therapy is smaller in magnitude than that observed with oestrogen alone.

### ***Ovarian cancer***

At the time of the current review there was no level I or II evidence available relating to ovarian cancer risk. However, since then, ovarian cancer results from the WHI study (level II evidence) have become available showing no increased risk (see Addendum A). Previous level III-2 evidence suggested an increased risk of both ovarian cancer incidence and mortality with oestrogen-only HRT, that became more pronounced with longer duration therapy.

### ***Cardiovascular disease***

#### **Women in general**

An existing high quality systematic review found no association between HRT and CVD incidence or CVD death in women with no prior CVD. There is some level III evidence that oestrogen-only but not combined HRT reduces the risk of CVD in this population. However, on balance, the evidence suggests that HRT does not provide primary protection against CVD. At present, there is insufficient evidence to determine the effects of different routes of administration or duration of HRT upon CVD.

#### **Women with existing cardiovascular disease**

There is level II evidence which indicates no association between risk of CVD death and oestrogen-only or combined HRT in women with existing CVD. At present, there is insufficient evidence to draw any conclusions regarding the effect of different types, administration or duration of HRT on CVD incidence in this population.

## **Coronary artery disease**

### **Women in general**

An existing systematic review and higher quality RCTs indicate that HRT has no impact upon the likelihood of CAD events, although isolated observational studies do show some benefit. On balance, the evidence suggests that HRT does not offer primary protection against CAD. At present, there is insufficient evidence to determine the effects of different types, administration or duration of HRT upon CAD.

### **Women with existing cardiovascular disease**

Evidence from high quality randomised controlled trials, supported by observational studies, indicates no benefit of HRT for the secondary prevention of CAD. In fact there is some suggestion from the observational studies, that commencing HRT use subsequent to a myocardial infarction (MI) may result in an elevation of risk of recurrence of CAD events. Limited information suggests that the magnitude of the risk increase may be greater in the time period immediately after the initial cardiac event.

## **Stroke**

### **Women in general**

Evidence from an existing systematic review and a large, high quality, randomised, controlled trial indicates an increased risk of stroke with HRT. There is some level III evidence indicating that this increased risk is dose-dependent with respect to oestrogen. In addition, there is a suggestion amongst the level III evidence that the magnitude of the increased risk may be greatest in the first 6–12 months of HRT use.

### **Women with existing cardiovascular disease**

Evidence from three large, high quality RCTs indicates there is no significant association between risk of stroke and HRT in women with existing CVD. At present, there is insufficient evidence to determine the effects of different types, administration or duration of HRT upon the risk of stroke in this population.

## **Venous Thromboembolism**

### **Women in general**

Evidence from existing systematic reviews and a large, high quality, randomised, controlled trial indicates an increased risk of venous thromboembolism for women in general who are receiving HRT. The magnitude of the elevation in risk appears to be substantial. At present, there is insufficient evidence to determine the effects of different types, administration or duration of HRT upon the risk of venous thromboembolism.

### **Women with existing cardiovascular disease**

Evidence from large, high quality RCTs indicates an increased risk of venous thromboembolism amongst women with previous CVD who take HRT. Furthermore, the magnitude of the elevation in risk appears to be substantial (2-3-fold). At present, it is not possible to confidently determine differential effects of combined HRT versus oestrogen-only HRT.

## **Cholecystitis/cholecystectomy**

Level II evidence from a recent high quality study showed no statistically significant increased risk of gallbladder disease and biliary tract surgery with combined HRT, when the results were adjusted for statin use. However, this study was limited to a specific population of older women with existing cardiovascular disease who have an increased risk of gall bladder disease at baseline relative to younger, healthier postmenopausal women. This contrasts with the findings of an older observational study, which reported a statistically significant increased risk of cholecystitis with HRT use. At present, there is insufficient evidence to determine the effects of different types, administration or duration of HRT upon cholecystitis.

## Mammography

Insufficient information is available to reliably determine the impact of HRT use upon the diagnostic performance of mammography. All but one of the studies included in the recent systematic review failed to adjust for important confounding factors, such as age and menopause status, and therefore the findings are difficult to interpret. Furthermore, the emerging impact of HRT use upon breast cancer incidence *per se* has the potential to independently account for the findings, as the methodology relies upon all interval cancers being assigned as false negative diagnoses from the preceding mammography visit.

## TIBOLONE

There is consistent level I and II evidence that tibolone is more effective than placebo or no treatment, and of equal efficacy to HRT in the treatment of vasomotor and urogenital symptoms. There is limited and conflicting level II evidence that tibolone has an effect on sexual function or sleep disturbances. There is limited level II evidence that tibolone improves global quality of life, but no evidence regarding the effectiveness of tibolone according to menopause-specific global symptom scales. There is level I and II evidence which suggests that while tibolone does cause bleeding, particularly in the early stages of treatment, it is associated with a lower incidence of bleeding than either ERT or continuous EPRT.

## RALOXIFENE

There is level II evidence in osteoporotic women that raloxifene decreases the risk of new vertebral fractures, but has no effect on the risk of non-vertebral fractures.

While the risks associated with raloxifene were not specifically examined by this review, there is some level II evidence that raloxifene decreases the risk of breast cancer, and decreases the risk of cardiovascular events in women with existing increased cardiovascular risk, but has no effect on cardiovascular event rates in women in general. There is level II evidence that raloxifene does not alter the risk of endometrial cancer, but that it does significantly increase the risk of VTE. Raloxifene does not appear to increase vaginal bleeding.

## CAMs

There is some conflicting level II evidence that soy and soy products improve vasomotor and urogenital symptoms, and limited level II evidence that soy protein has no effect on sleep disturbances. There is level I evidence that soy and soy products have no significant impact on global menopausal symptom or quality of life scales.

There is level II evidence that red clover (Promensil), dong quai, Evening Primrose oil, ginseng and a Chinese herb mixture have no effect on vasomotor symptoms, and a paucity of good quality evidence regarding the efficacy of black cohosh (Remifemin) against vasomotor symptoms. There is no evidence regarding the effect of these herbs on sleep disturbances, and limited level II evidence that dong quai has no effect on urogenital symptoms.

There is conflicting level II evidence that black cohosh is as efficacious as HRT at relieving menopausal symptoms and improving quality of life. However, there is limited level II evidence that red clover, dong quai, ginseng and a Chinese herb mixture have no significant effect on global menopausal symptom or quality of life scales.

## 5 ADDENDUM A: OESTROGEN IN COMBINATION WITH TESTOSTERONE

Two studies were identified which examined the effect of a combination of oestrogen plus testosterone on relieving sexual dysfunction. However, both of these studies were excluded on the basis that they were crossover studies with no washout period between treatments. While not formally included in the systematic review, their results will be briefly described here.

The double-blind RCT by Shifren *et al.* (2000) examined the effect of two different doses of transdermal testosterone (150 µg and 300 µg) in combination with oral conjugated equine oestrogen (at least 0.625 mg) compared with oestrogen plus placebo in women with impaired sexual function after oophorectomy. There were 25 women in each treatment arm. The results showed that oestrogen plus testosterone generally had a similar efficacy at relieving sexual symptoms compared with oestrogen plus placebo. However, the high dose of testosterone (300 µg) significantly increased the following sub-scores of the Brief Index of Sexual Functioning for Women compared with placebo: composite score, frequency of sexual activity and pleasure – orgasm. Similarly, only the 300 µg dose of testosterone improved certain sub-scores on the Psychological Well-being Index including the composite score and depressed mood and positive well-being scores. Testosterone-related side effects including hirsutism and acne did not change significantly during treatment with the exception of facial depilation in the high dose testosterone group.

In the double-blind RCT by Floter *et al.* (2002), oestradiol valerate (2 mg) plus testosterone undecanoate (40 mg) was compared with oestradiol valerate plus placebo in surgically menopausal women. There were 25 women in each treatment arm. The author's found that the addition of testosterone to oestradiol significantly improved some aspects of sexual function (as measured by the McCoy sex scale questionnaire) compared with oestradiol alone (enjoyment of sex, satisfaction of frequency of sexual activity, interest in sex and the total score). There was no difference between treatments on any aspect of the Psychological Well-being index. Testosterone-related side effects (hirsutism and acne) were mild and were experienced by a similar number of women in the testosterone and placebo groups.

The results of both of these studies should be considered in the context of the study design. Both studies used a crossover design with no washout between different treatment periods. It is not possible to confirm whether there is any difference between oestrogen alone and oestrogen plus testosterone on the basis of these studies alone. The lack of effect reported in these studies may be due to a carry-over effect or a lack of power due to the small sample size.

## 6 ADDENDUM B: UPDATED AND NEW STUDY RESULTS

Since the literature search conducted in May 2003, there have been a number of important publications regarding the risks and benefits of the use of HRT in postmenopausal women. The majority of these have represented updated or new analyses of data from the Women's Health Initiative (WHI) study, a large RCT. The other relates to a large cohort study conducted in the United Kingdom, the Million Women Study. This section includes a summary of the results published in these recent updated or new analyses.

### Women's Health Initiative Study

The WHI study is a large RCT comparing a combined HRT regimen (continuous conjugated equine oestrogen plus medroxyprogesterone acetate) to placebo in 16 608 postmenopausal women with an intact uterus. The trial, conducted at 40 sites in the United States, was originally planned to run for 8.5 years. However, after an interim safety analysis revealed an unacceptably high risk of breast cancer in the subjects taking HRT, the trial was stopped early after 5.2 years of follow-up. It should be noted that a comparison of ERT with placebo is ongoing and is due to finish in 2005.

Since the publication of the main study results (Rossouw *et al*, 2002), which are included in the current review, a number of further analyses have been published. The results of the updated analyses published since the literature search conducted in May 2003 are summarised in Table 206 and Figure 81. The updated results do not substantially differ from those WHI results already included in the review for endometrial cancer and cardiovascular disease. However, the results for osteoporosis are somewhat different to those reported in the original analysis which showed that HRT did not cause a statistically significant reduction in hip or vertebral fractures. In the updated analysis (Cauley *et al.*, 2003), statistically significant reductions in fracture risk were seen for all three sites examined (ie, hip, vertebral and lower arm/wrist).

TABLE 206 HRT: UPDATED RESULTS FROM THE WHI STUDY

Citation	Outcome	Follow-up	HRT n/N	Placebo n/N	Hazard ratio (95% CI)
<i>Osteoporotic fracture</i>					
Cauley <i>et al.</i> (2003)	Any fracture	5.6 years	733/8506	896/8102	<b>0.76 (0.69, 0.83)</b>
Cauley <i>et al.</i> (2003)	Hip fracture	5.6 years	nr	nr	<b>0.67 (0.47, 0.96)</b>
Cauley <i>et al.</i> (2003)	Vertebral fracture	5.6 years	nr	nr	<b>0.65 (0.46, 0.92)</b>
Cauley <i>et al.</i> (2003)	Lower arm/wrist fracture	5.6 years	nr	nr	<b>0.71 (0.59, 0.85)</b>
<i>Cancer</i>					
Anderson <i>et al.</i> (2003)	Endometrial cancer	5.6 years	27/8506	31/8102	0.81 (0.40, 1.64) <sup>a</sup>
<i>Cardiovascular disease</i>					
Manson <i>et al.</i> (2003)	CHD <sup>b</sup>	5.2 years	188/8506	147/8102	1.24 (1.00, 1.54) <sup>c</sup> 1.24 (0.97, 1.60) <sup>d</sup>
Manson <i>et al.</i> (2003)	All nonfatal MI	5.2 years	151/8506	114/8102	1.28 (1.00, 1.63) <sup>c</sup> 1.28 (0.96, 1.70) <sup>d</sup>
Manson <i>et al.</i> (2003)	CHD death	5.2 years	39/8506	34/8102	1.10 (0.70, 1.75) <sup>c</sup> 1.10 (0.65, 1.89) <sup>d</sup>
Wassertheil-Smoller <i>et al.</i> (2003)	Total stroke	5.6 years	151/8506	107/8102	<b>1.31 (1.02, 1.68) <sup>e</sup></b>
Wassertheil-Smoller <i>et al.</i> (2003)	Ischaemic stroke	5.6 years	125/8506	81/8102	<b>1.44 (1.09, 1.90)</b>
Wassertheil-Smoller <i>et al.</i> (2003)	Haemorrhagic stroke	5.6 years	18/8506	20/8102	0.82 (0.43, 1.56)

Note: Risk estimates in italics are considered statistically significant as they do not include one.

Abbreviations: CHD, coronary heart disease; CI, confidence interval; HR, hazard ratio.

<sup>a</sup> 95% CI adjusted for multiple outcomes.

<sup>b</sup> Includes acute MI necessitating hospitalisation, silent MI as determined by serial ECG and death due to CHD.

<sup>c</sup> Nominal 95% CI

<sup>d</sup> 95% CI adjusted for sequential monitoring

<sup>e</sup> Stratified by age, previous stroke and diabetes mellitus randomisation assignment. Similar results were seen for the ITT analysis when adjusted for other covariates. A slightly higher increased risk (~ 50%) seen when adjusted for adherence also.

In addition, recent publications have presented WHI results for several included outcomes that were not available at the time of the review (Table 207 and Figure 81). The results of Anderson *et al.* (2003) show no significant effect of combined HRT upon ovarian cancer. As there was previously no level II evidence available, this new data represents the highest level of evidence. The level III-2 evidence included in the body of the review was somewhat inconsistent, although it was suggestive of an increased risk of ovarian cancer.

For the analysis of cognition in the WHI study, a sub-study was carried out. Of the total population recruited to the WHI study, 4532 women aged > 65 years and free of probable dementia were recruited to the Women's Health Initiative Memory Study (WHIMS). The primary outcome for this sub-study was the incidence of probable dementia (all types), with mild cognitive impairment and global cognitive functioning as secondary outcomes. Each of these outcomes was identified using the Modified Mini-Mental State Examination (MMSE). All participants completed the MMSE at baseline, and annually thereafter. The mean duration of follow-up of WHIMS was 4.05 years.

Subjects with MMSE scores  $\leq 72$  (for subjects with  $\leq 8$  years of education) or of  $\leq 76$  (for subjects with  $> 9$  years of education) underwent further neuropsychological tests to determine if mild cognitive impairment or dementia was present. During the study, the MMSE threshold scores were changed prospectively to  $\leq 80$  (subjects with  $\leq 8$  years education) and  $\leq 88$  (for subjects with  $> 9$  years of education). Final diagnosis of no dementia, mild cognitive impairment or probable dementia was based on DSM-IV criteria, and undertaken by specialist clinicians blinded to treatment assignment.

The publication by Shumaker *et al.* (2003) reported a significant two-fold increase in the risk of dementia among women randomised to HRT versus placebo, as shown in Table 207. Evidence of an increased risk began to appear as early as one year after randomisation. In women who reported no prior HRT use, the hazard ratio was 1.98 (95% CI: 1.13, 3.47). The results are in contrast to most of the earlier research on the effects of HRT on AD and dementia (see Cognition/Dementia section). However, as stated by the authors, the absolute number of cases of dementia was small, and in keeping with both the age of the cohort and 'healthy-user bias'.

In the WHIMS, there was no difference between groups in the incidence of mild cognitive impairment (see Table 207). This observation appears to be inconsistent with the conclusion that HRT enhances the rate of progression to dementia. However, Shumaker *et al.* (2003) conclude that mild cognitive impairment is not predictive of probable dementia, and suggest this relates to heterogeneity in the underlying diseases among participants with mild cognitive impairment as opposed to dementia.

A companion publication from the WHIMS (Rapp *et al.*, 2003) reported that EPRT did not improve cognitive function when compared with placebo. This is consistent with earlier research where improvements in cognitive function were typically observed in symptomatic postmenopausal women (ie, women in the WHIMS were  $\geq 65$  years and unlikely to be symptomatic).

TABLE 207 HRT: NEW RESULTS FROM THE WHI STUDY

Citation	Outcome	Follow-up	HRT n/N	Placebo n/N	Hazard ratio (95% CI)
<i>Ovarian cancer</i>					
Anderson <i>et al.</i> (2003)	Invasive ovarian cancer	5.6 years	20/8506	12/8102	1.58 (0.59, 4.23)
<i>Cognition</i>					
Shumaker <i>et al.</i> (2003)	Probable dementia (all types) <sup>a</sup>	~ 4 years	45/10 000 py <sup>b</sup>	22/10 000 py <sup>b</sup>	<b>2.05 (1.21, 3.48)</b>
Shumaker <i>et al.</i> (2003)	Mild cognitive impairment	~ 4 years	63/10 000 py	59/10 000 py	1.07 (0.74, 1.55)
			Rate of change Mean (SE)	Rate of change Mean (SE)	Mean difference (95% CI)
Rapp <i>et al.</i> (2003)	Cognition <sup>c</sup>	4.2 years	N=2145 0.149 (0.021)	N=2236 0.213 (0.020)	<b>-0.063 (-0.120, -0.006)</b>

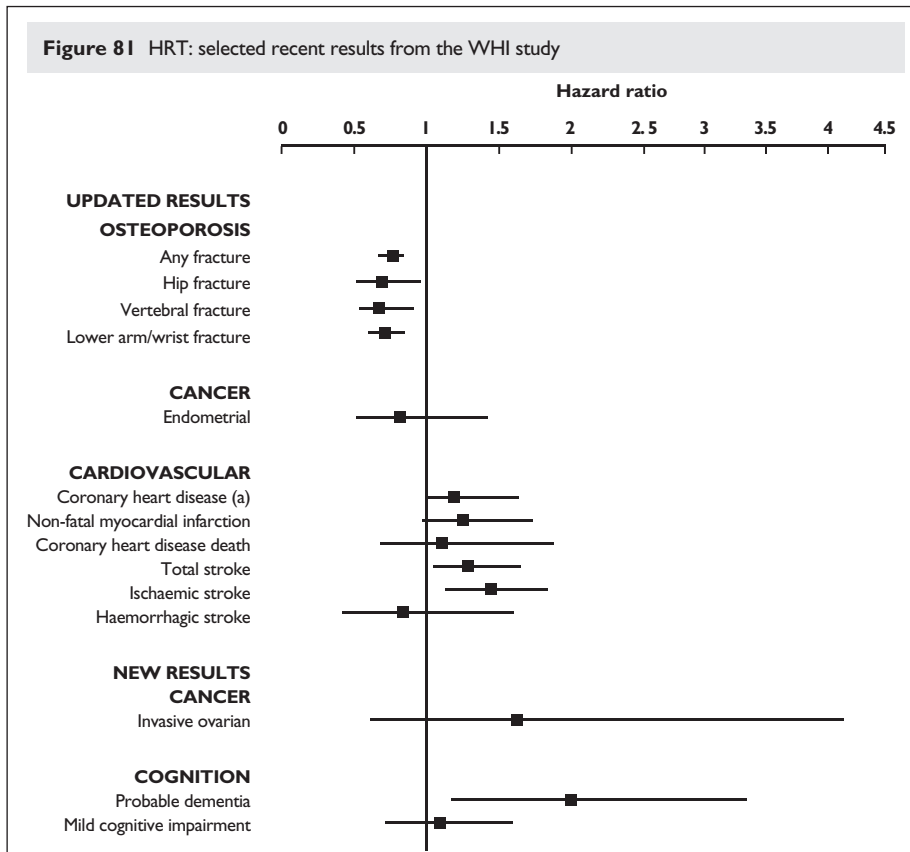
Note: Risk estimates in italics are considered statistically significant as they do not include one (for hazard ratio) or zero (for mean difference).

Abbreviations: CI, confidence interval; HR, hazard ratio; SE, standard error.

<sup>a</sup> Of the probable dementia cases, 20/40 and 12/21 in the EPRT and placebo arms respectively were classified as AD.

<sup>b</sup> In HRT arm 20/40 cases of dementia classified as Alzheimer disease compared with 12/21 in the placebo arm.

<sup>c</sup> Measured by the Modified Mini-Mental State Examination



## Million Women Study

The Million Women Study is a large cohort study including 1 084 110 UK women recruited between 1995 and 2001. Women were recruited at the time they were due for a routine mammography and provided information regarding their menopausal status and HRT use. Data was also collected for a number of potential confounding factors. Analyses were stratified by age and adjusted for time since menopause, childbearing history, age at first birth, family history of breast cancer, BMI, geographical region and deprivation index. Women were followed-up for a mean 2.6 years for breast cancer incidence data and 4.1 years for breast cancer mortality data. The main analysis of the association between HRT and breast cancer risk and mortality was conducted in a subset of 828 923 women who were postmenopausal at baseline, with a defined time since menopause.

The endpoints examined in the study were first diagnosis of invasive breast cancer and death due to breast cancer. Outcomes were measured by flagging study participants on cancer registries so that investigators would be routinely notified of relevant events.

As a cohort study, the Million Women Study constitutes level III-2 evidence, and is subject to the many biases inherent in observational studies. While one of the positive aspects of the study is its size, and hence its ability to examine a wide range of types of HRT (including different modes of administration), there are a number of flaws which limit the interpretation and generalisability of the study's findings. These include the potential for misclassification resulting from the collection of HRT data at baseline based on subject recall and the short period of follow-up. Therefore, the following results should be viewed with these factors in mind.

The main results of this analysis are summarised in Table 208 and Figure 82. These results suggest that the risk of developing or dying from breast cancer was significantly increased in women who were taking HRT at baseline. More detailed analyses based on recency of use, duration of use and type of HRT used follows.

TABLE 208 HRT: RESULTS FROM THE MILLION WOMEN STUDY – BREAST CANCER INCIDENCE AND MORTALITY

Outcome	HRT n/N	No HRT n/N	Relative risk <sup>a</sup> (95% CI)
<i>Breast cancer incidence</i>			
Ever-use	nr	nr	<i>1.43 (1.36, 1.50)</i>
Current-use	3202/285 987	2894/392 757	<i>1.66 (1.60, 1.72)</i>
Past-use	1044/150 179	2894/392 757	1.01 (0.95, 1.08)
<i>Breast cancer mortality</i>			
Ever-use	nr	nr	nr
Current-use	191/285 987	238/392 757	<i>1.22 (1.05, 1.41)</i>
Past-use	88/150 179	238/392 757	1.05 (0.85, 1.29)

Note: Risk estimates in italics are considered statistically significant as they do not include one.

Abbreviations: CI, confidence interval; nr, not reported.

<sup>a</sup> Stratified by age, time since menopause, parity and age at first birth, family history of breast cancer, BMI, region and deprivation index.

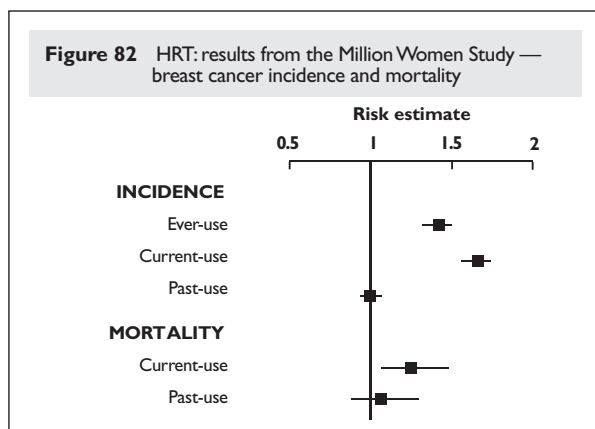


Table 209 and Figure 83 show the results of the analysis of past use of HRT including time since last use and duration of past use. These results suggest that the elevated risk of breast cancer associated with HRT may diminish over time.

TABLE 209 HRT: RESULTS FROM THE MILLION WOMEN STUDY – BREAST CANCER INCIDENCE BASED ON PAST-USE

Outcome	HRT n/N	No HRT n/N	Relative risk <sup>a</sup> (95% CI)
Past-use - incidence	1044/150 179	2894/392 757	1.01 (0.95, 1.08)
< 5 years ago	579/81 875	2894/392 757	1.04 (0.95, 1.12)
5-9 years ago	207/29 395	2894/392 757	1.01 (0.88, 1.16)
≥ 10 years ago	79/12 568	2894/392 757	0.90 (0.72, 1.12)
< 1 year duration	311/47 606	2894/392 757	0.94 (0.84, 1.05)
1-4 years duration	384/55 823	2894/392 757	1.01 (0.92, 1.12)
5-9 years duration	230/29 614	2894/392 757	1.14 (1.00, 1.30)
≥ 10 years duration	80/11 654	2894/392 757	1.05 (0.84, 1.30)

Note: Risk estimates in italics are considered statistically significant as they do not include one.

Abbreviations: CI, confidence interval.

<sup>a</sup> Stratified by age, time since menopause, parity and age at first birth, family history of breast cancer, BMI, region and deprivation index.

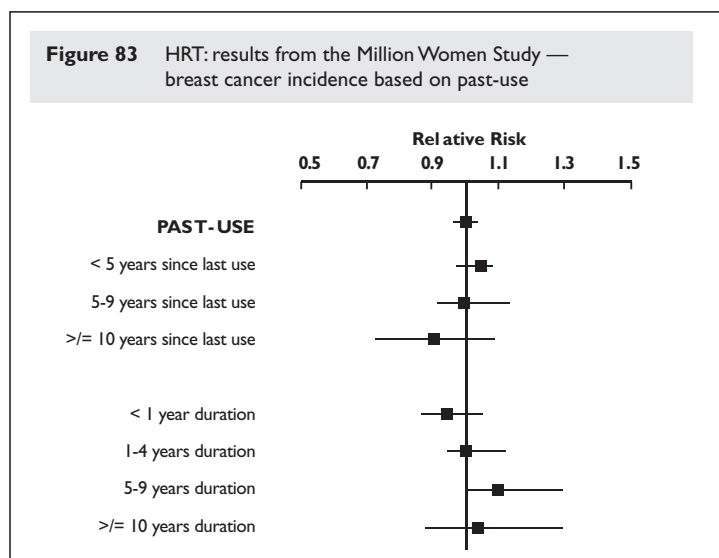


Table 210 and Figure 84 show the results of the analysis oestrogen-only therapy. These results show that ever- or current-use of oestrogen-only therapy is associated with an increased risk of breast cancer, regardless of type or mode of administration (oral, transdermal or implant) or duration, with one exception. Current-use of oestrogen-only therapy for less than one year showed no significant increase in breast cancer risk, implying that risk may increase with increased duration of HRT use. The magnitude of increased risk was relatively constant (~ 1.2 – 1.6 times)

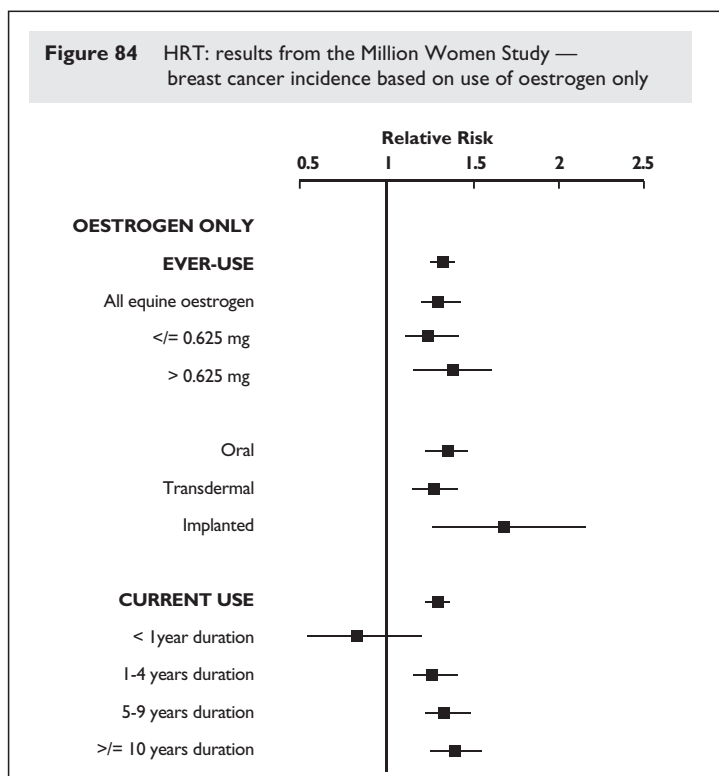
TABLE 210 HRT: RESULTS FROM THE MILLION WOMEN STUDY – BREAST CANCER INCIDENCE BASED ON USE OF OESTROGEN ONLY

Outcome	HRT n/N	No HRT n/N	Relative risk <sup>a</sup> (95% CI)
Oestrogen-only			
Ever-use	991/115 383	2894/392 757	1.30 (1.21, 1.40)
All equine oestrogen	426/48 386		1.29 (1.16, 1.43)
≤ 0.625 mg equine oestrogen	288/33 039		1.25 (1.11, 1.41)
> 0.625 mg equine oestrogen	135/15 181		1.36 (1.14, 1.61)
Oral	606/68 351		1.32 (1.21, 1.45)
Transdermal	324/40 015		1.24 (1.11, 1.39)
Implanted	54/5272		1.65 (1.26, 2.16)
Current-use	991/115 383		1.30 (1.22, 1.38)
< 1 year duration	25/4452		0.81 (0.55, 1.20)
1-4 years duration	251/29582		1.25 (1.10, 1.41)
5-9 years duration	416/47310	1.32 (1.20, 1.46)	
≥ 10 years duration	277/31 862	1.37 (1.22, 1.54)	

Note: Risk estimates in italics are considered statistically significant as they do not include one.

Abbreviations: CI, confidence interval.

<sup>a</sup> Stratified by age, time since menopause, parity and age at first birth, family history of breast cancer, BMI, region and deprivation index.



Use of oestrogen plus progestogen therapy resulted in a significantly increased risk of breast cancer. This finding was unchanged when analyses were performed based on type of progestogen, regimen or duration of ever- or current-use. These results are summarised in Table 211 and Figure 85.

The magnitude of increased risk appears to be greater than with oestrogen alone (~ 1.6 times with < 5 years use and 2 times with > 5 years use). However, as this is a cohort study, it is not entirely appropriate to make a direct comparison as the underlying breast cancer risk may have differed between HRT groups.

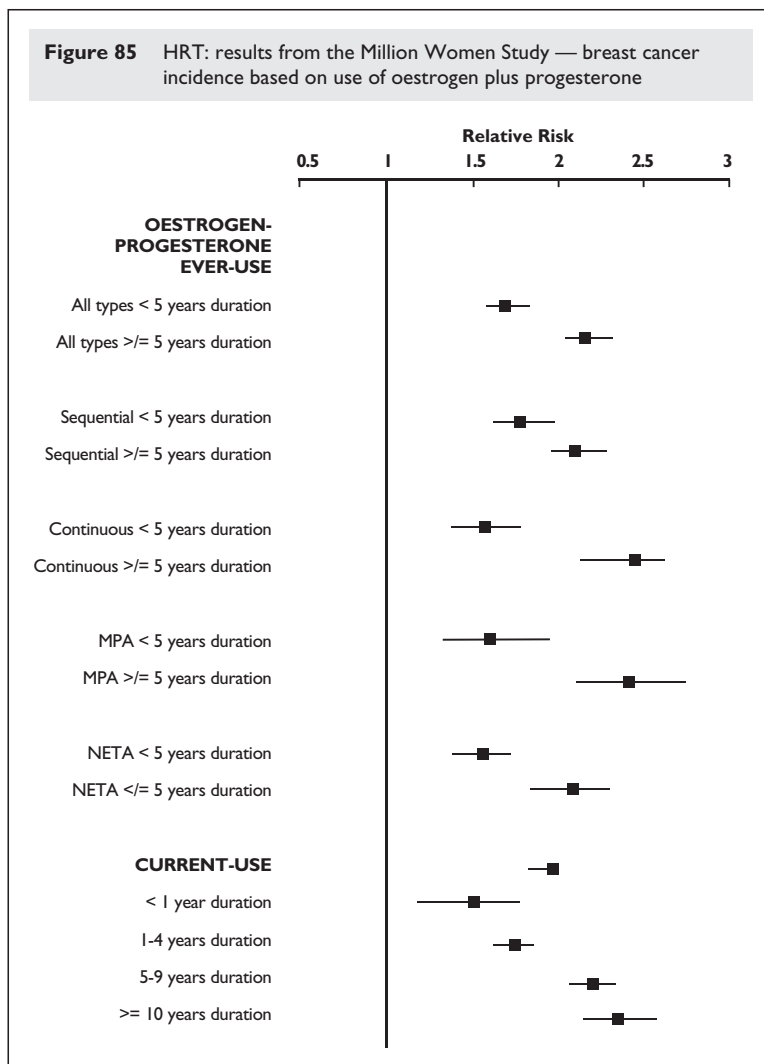
TABLE 211 HRT: RESULTS FROM THE MILLION WOMEN STUDY – BREAST CANCER INCIDENCE BASED ON USE OF OESTROGEN PLUS PROGESTERONE

Outcome	HRT n/N	No HRT n/N	Relative risk <sup>a</sup> (95% CI)
Oestrogen-progestogen			
Ever-use	1934/142 870		2.00 (1.91, 2.09)
All types < 5 years duration	679/59 011		1.70 (1.56, 1.86)
All types ≥ 5 years duration	1212/80 585		2.21 (2.06, 2.36)
Sequential < 5 years duration	403/33 124		1.77 (1.59, 1.97)
Sequential ≥ 5 years duration	778/52 518		2.12 (1.95, 2.30)
Continuous < 5 years duration	243/23 708		1.57 (1.37, 1.79)
Continuous ≥ 5 years duration	388/25 286		2.40 (2.15, 2.67)
MPA < 5 years duration	117/11 280	2894/392 757	1.60 (1.33, 1.93)
MPA ≥ 5 years duration	196/12 628		2.42 (2.10, 2.80)
NETA < 5 years duration	253/24 667		1.53 (1.35, 1.75)
NETA ≥ 5 years duration	390/27 841		2.10 (1.89, 2.34)
Current-use	1934/142 870		2.00 (1.91, 2.09)
< 1 year duration	97/9771		1.45 (1.19, 1.78)
1-4 years duration	582/49 240		1.74 (1.60, 1.89)
5-9 years duration	850/56 912		2.17 (2.03, 2.33)
≥ 10 years duration	362/23 673		2.31 (2.08, 2.56)

Note: Risk estimates in italics are considered statistically significant as they do not include one.

Abbreviations: CI, confidence interval; MPA, medroxyprogesterone; NETA, norethisterone acetate.

<sup>a</sup> Stratified by age, time since menopause, parity and age at first birth, family history of breast cancer, BMI, region and deprivation index.



Finally, current-use of tibolone was associated with an increased risk of breast cancer, similar to that seen for HRT. A longer duration of therapy was associated with a greater risk. Past-use of tibolone was not associated with increased risk of breast cancer. It should be noted that the actual numbers of breast cancer cases were not available for some of these analyses. These results are summarised in Table 212 and Figure 86.

The magnitude of the risk appears to be comparable to oestrogen-alone HRT (ie, lower than that observed for combined HRT). Once again, it may not be appropriate to compare between HRT groups in a cohort study as the underlying breast cancer risk may differ between groups.

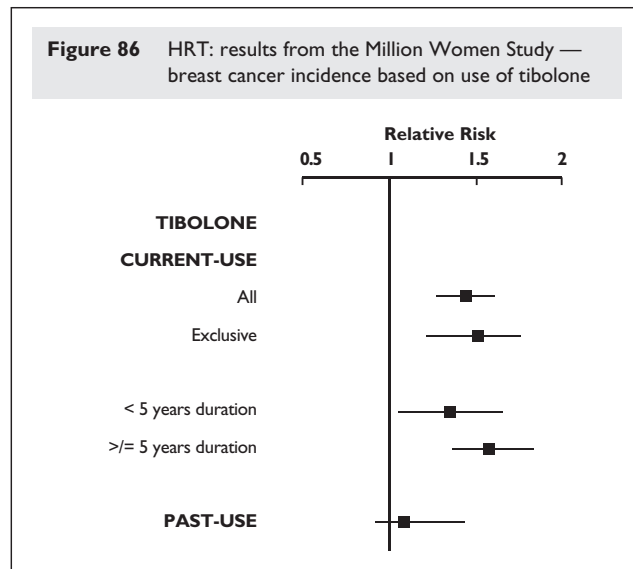
TABLE 212 HRT: RESULTS FROM THE MILLION WOMEN STUDY – BREAST CANCER INCIDENCE BASED ON USE OF TIBOLONE

Outcome	HRT n/N	No HRT n/N	Relative risk <sup>a</sup> (95% CI)
Current-use			
All	184/18186		<i>1.45 (1.25, 1.67)</i>
Exclusive	nr		<i>1.48 (1.20, 1.83)</i>
< 5 years duration	nr	2894/392 757	<i>1.32 (1.04, 1.69)</i>
≥ 5 years duration	nr		<i>1.57 (1.30, 1.90)</i>
Past-use	nr		1.08 (0.82, 1.42)

Note: Risk estimates in italics are considered statistically significant as they do not include one.

Abbreviations: CI, confidence interval.

<sup>a</sup> Stratified by age, time since menopause, parity and age at first birth, family history of breast cancer, BMI, region and deprivation index.



In summary, the authors of the Million Women Study conclude that “current use of HRT is associated with an increased risk of incident and fatal breast cancer; the effect is substantially greater for oestrogen-progestogen combinations than for other types of HRT”.

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