Evaluation of the benefits and risks of hormone replacement therapy

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Objective. To review recent data on outcome of hormone replacement therapy in postmenopausal women.
Data sources. *Medline* search of the literature and local data.
Study selection. Data on efficacy of hormone replacement and its unwanted side effects were examined.
Data extraction. Statistical data were extracted from published studies and meta-analyses.
Data synthesis. Statistical data came mainly from observational studies and not from randomised trials, and were therefore subject to bias. Overall, it would appear reasonable to say that risks for breast and endometrial cancers, as well as thromboembolism, were increased, while the risks for cardiovascular death and osteoporotic fractures were reduced by hormone replacement therapy. Locally, for every 100 000 women treated for 3 to 5 years, there may be 22 fewer cardiac deaths, 10 to 20 more cases of breast cancer, seven more cases of endometrial cancer, 10 more cases of thromboembolic disease, and slightly fewer cases of osteoporotic fracture.
Conclusion. Reported data and risk estimates have been derived predominantly from data on white Caucasian women. Their baseline risk may be different from those of Chinese women. A low baseline risk in the local population may influence treatment results, and large-scale randomised trials are needed to give a definitive answer.

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Key words: Estrogen replacement therapy; Estrogens/conjugated; Menopause/drug effects; Risk factors

Introduction

Hormone replacement therapy (HRT) has been increasingly prescribed in the United States for postmenopausal symptoms since the 1960s.[1] A decade later, studies showed that HRT was associated with a decreased risk of ischaemic heart disease (IHD)[2-7] and osteoporotic fractures.[8] At about the same time, there were reports of an increased risk of endometrial[9-13] and breast[14-17] cancers, as well as conflicting reports on thromboembolic risk in women taking oestrogen for contraception or replacement therapy.[18-20] As a result, the pattern in the method by which HRT was given changed from HRT with unopposed oestrogen alone (E-HRT), to combination oestrogen-progestogen HRT (EP-HRT), taken either sequentially, or continuously.[21] Recent reports and meta-analyses that detail the various risks and benefits for the different regimens have included data from many of the older publications, very few of which were randomised studies. This review examines recent reports with several end-points in mind, such as risks of cancer, ischaemic heart disease, osteoporosis, thromboembolism, and the risk of hormone-dependent cancers. The changes resulting from HRT in the relative risks (RRs) for the various end-points, together with their respective 95% confidence intervals (CIs) were extracted from overseas publications. Baseline risks were extracted from local sources and overseas publications.

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Cardiovascular disease

In 1998, figures from the Government of Hong Kong Special Administrative Region showed that the number of deaths from heart disease in Hong Kong was 75 per 100 000 population, compared with 159 per 100 000 for malignant diseases.[22] For a 50-year-old Caucasian woman, the Clinical Efficacy Assessment Subcommittee (CEAS) in the United States estimated a 46% lifetime risk of the development of IHD, and a 31% lifetime probability of dying from IHD.[23] The estimated median age at the time of death from IHD was 74 years.[23]

Table 1. Ischaemic heart disease and hormone replacement therapy

Study	Relative risk (95% CI)	
	Oestrogen	Oestrogen/progestogen
Grady et al,[23] 1992	0.65 (0.59-0.71)*	-
Barrett-Connor and Grady,[24] 1998	0.70 (0.65-0.75)*	0.66 (0.53-0.84)*
Hemminki and McPherson,[27] 1997 (odds ratio)	1.39† (0.48-3.95)	-
Hulley et al,[31] 1998 (relative hazard)	0.99† (0.80-1.22)	-

* Relative risk for women who have ever used hormone replacement therapy
† Placebo-controlled, in patients with existing ischaemic heart disease

Since the initial reports that showed a beneficial effect of HRT on the risk of IHD, some meta-analyses have been published (Table 1). Comparing women who had used or never used HRT, summary estimates of RR after E-HRT were reported as 0.65 (95% CI, 0.59-0.71) by the University of California, San Francisco,[23] and 0.70 (95% CI, 0.65-0.75) by the University of California, San Diego.[24] For EP-HRT, the RR was 0.66 (95% CI, 0.53-0.84).[24] Summary estimates of the relative risk of death from IHD was 0.63 (95% CI, 0.55-0.72).[23] Data from these two reports were not sufficient to examine the effect of hormone dosage or duration of use on risk of IHD. Overall, when compared with never users, E-HRT[25,26] and EP-HRT[23,24] users had a reduced risk of IHD of about 30%. There was, however, one report from Helsinki of pooled data from other placebo-controlled trials (in which cardiovascular events was not a specific end point), which showed that women taking HRT had a statistically non-significant increase in risk of IHD.[27]

In the general population, meta-analyses of studies on predominantly white Caucasian women have shown that HRT probably reduces the risk of IHD by about 30%.[23,24,28,29] However, these data came from observational studies and not from randomised trials, and they were thus subject to bias, which could have exaggerated the beneficial effects of the treatment,[23,24] resulting from, for example, prescribing HRT only to healthy women.[28,29]

For women with a pre-existing history of IHD or who are at increased risk for the development of IHD, one study has suggested a beneficial effect and an approximate 2-year increase in mean life expectancy with HRT.[30] The Heart and Estrogen/Progestin Replacement Study (HERS),[31] however, reported no difference between placebo or EP-HRT in women with existing IHD (relative hazard = 0.99; 95% CI, 0.80-1.22). In fact, the risk may be increased during the first year of HRT in this group. The average follow-up of women in this report was 4 years, and 75% of women assigned to hormone treatment were still taking it at the end of 3 years.

There have also been many reports on the beneficial effects of HRT on serum lipids and coagulation factors,[32-35] which theoretically should lead to a reduced risk of death from IHD. The Postmenopausal Estrogen/Progestin Interventions (PEPI) trial,[36] for example, showed that HRT improved lipoproteins and lowered fibrinogen levels, with E-HRT resulting in the greatest increase in high-density lipoprotein–cholesterol. The Heart and Estrogen/Progestin Replacement Study (HERS),[31] however, failed to show any difference between EP-HRT and placebo in women with existing IHD, even though the EP-HRT group had an 11% lower level of low-density lipoprotein–cholesterol and a 10% higher level of high-density lipoprotein–cholesterol after an average follow up of 4 years. Results from more randomised studies are needed to confirm the findings of meta-analyses of observational studies.

Breast cancer

There have been many reports on breast cancer risk arising from HRT. Several questions need to be answered. Does HRT increase the risk of breast cancer? Is there any difference between E-HRT and EP-HRT? Is the risk related to the dose and duration of use, and is it a persistent risk? Recent reports have provided some answers (Table 2).[37-39]

The meta-analysis from the Collaborative Group on Hormonal Factors in Breast Cancer[37] included women on HRT whose median age at first use was 48 years, and among whom 34% received HRT for longer than 5 years. In women who had stopped HRT for 5 years or longer, there was no overall excess of breast cancer risk. For current HRT users, as well as those who stopped HRT less than 4 years previously, the RR for breast cancer was 1.023 per year of use (95% CI, 1.011-1.036)—that is, an increased risk of 2.3% per year of use. Increasing duration of HRT was associated with an increasing breast cancer risk: for women using HRT for more than 5 years, the RR was 1.35 (95% CI, 1.21-1.49) and the average duration of HRT in the studies included in this analysis was 11 years. The increase in risk with longer duration of

Table 2. Risk of breast cancer in current users* of hormone replacement therapy

Study	Relative risk (95% CI)		Increased risk with longer use?
Collaborative Group on Hormonal Factors in Breast Cancer,[37] 1997 (for >5 years' use)	1.35 (1.21-1.49)		Yes
Ross et al,[38] 2000 (Odds ratio per 5 years' use)	1.10 (1.02-1.18)†		Yes
	Oestrogen	Oestrogen/progestogen	
Schairer et al,[39] 2000	1.20 (1.0-1.4)	1.40 (1.1-1.8)	Yes
Ross et al,[38] 2000 (per 5 years' use) sequential oestrogen/progestogen concurrent oestrogen/progestogen	1.06 (0.97-1.15)†	1.24 (1.07-1.45) 1.38 (1.13-1.68) 1.09 (0.88-1.35)	Yes

*Current users included those who stopped hormone replacement therapy <5 years previously, as well as those receiving therapy at the time of the study
†Use of hormone replacement therapy assessed to 1 year before study

use was greater in thin women (body mass index [BMI] less than 25 kg/m^2). The increase in breast cancer risk was comparable to a delayed menopause in women who have never used HRT, in whom the RR increase by 0.028 (95% CI, 1.021-1.034), or 2.8% for each year of delay. Another way of looking at the risk involved is the cumulative incidence of breast cancer in women who are aged 50 years and who live to the age of 70. For this group, the estimated cumulative incidence of breast cancer in the US and Europe was 45 per 1000 women. Use of HRT for 5, 10, or 15 years was estimated to result in an extra two, six, and twelve breast cancer cases, respectively, per 1000 women.[37] There was no definite evidence in this report about relative risks of E-HRT versus EP-HRT, although information on hormonal constituent was only available in one third of those included, and, of those, 80% used E-HRT.

The question of E-HRT versus EP-HRT in terms of breast cancer risk was recently addressed by a report from the Division of Cancer Epidemiology and Genetics of the National Cancer Institute.[39] In this cohort study, with a median follow up of 12 years, a statistically significant increased risk was seen in those who had had HRT in the previous 4 years. Treatment with E-HRT and EP-HRT resulted in relative risks for breast cancer of 1.2 (95% CI, 1.0-1.4) and 1.4 (95% CI, 1.1-1.8), respectively. The RR increased by 0.01 or 1% with each year of E-HRT (95% CI, 0.002-0.03), and by 0.08 or 8% for each year of EP-HRT (95% CI, 0.02-0.16). Among thin women (BMI ≤24.4 kg/m^2), the RR increased by 0.03 or 3% for each year of E-HRT (95% CI, 0.01-0.06), and by 0.12 or 12% for each year of EP-HRT (95% CI, 0.02-0.25). Risk was not increased in heavier women. Duration of use was also important. For E-HRT, the risk increase became significant after more than 8 years of use, and for EP-HRT, the risk increase became significant after more than 4 years of use.

Another group from the University of Southern California[38] confirmed this greater risk with EP-HRT in a population-based, case-control study. Use of E-HRT resulted in an odds ratio of 1.06 (95% CI, 0.97-1.15) for every 5 years of use, which was not statistically significant. In contrast, the RR for EP-HRT was significantly raised at 1.24 (95% CI, 1.07-1.45) for every 5 years of use. Overall, E-HRT increased the risk of breast cancer only after more than 15 years of use, (RR=1.24; or a 24% increase in risk), whereas EP-HRT significantly increased risk from 5 years onwards (OR=1.1 for 5 years of use; 1.51 for more than 10 years of use). The risk with sequential therapy (oestrogen followed by progestogen) may be higher than with continuous com-bined replacement therapy (OR=1.38; 95% CI, 1.13-1.68) versus concurrent therapy (OR=1.09; 95% CI, 0.88-1.35), but this difference was not statistically significant. The risk was higher in thin women but the report did not include the data in the report.

In the report from the Collaborative Group,[36] breast cancer in women who had used HRT tended to be less advanced (less likely to involve lymph nodes) compared with those who had never used HRT. The Iowa Women's Health Study—a prospective cohort study—found cancers of more favourable histology (ie mucinous, medullary, papillary carcinoma) in the HRT group.[40] The National Cancer Institute[39] showed the increased risk to be in invasive cancer, although the number of cases were too small to assess the risk of in situ disease. The group from the University of Southern California[38] showed that the excess risk seen with E-HRT was mainly for in situ cancers, whereas that for EP-HRT was for all types of breast cancers. Overall, there is a lack of definitive published evidence of a relationship between stage or aggressiveness of cancer and HRT.

Historically, there have been more women taking E-HRT than EP-HRT, as progestogen was added only

after the risk of endometrial cancer became apparent. This difference could have affected the published risk data. Nevertheless, existing evidence shows that there is an increased risk for breast cancer with increasing duration of HRT use, with EP-HRT having a higher risk than E-HRT. Thin individuals seem to be at increased risk. Use of HRT or E-HRT for more than 5 years increases the RR of cancer by <3% for each year of use, with a long-term overall increase of two extra cases of cancer per 1000 population. However, for thin individuals with a BMI <25 kg/m^2 and who are receiving EP-HRT, the relative risk is increased by 8% to 12% for each year of use. One should also bear in mind that for each case of breast cancer due to long-term E-HRT, more than six cardiac deaths may have been prevented.[41] Corresponding figures for EP-HRT are not available.

One should remember the difference in breast cancer risk between Hong Kong women and those overseas. Breast cancer risk is lower in Hong Kong, where the age-standardised incidence for breast cancer in 1996 was 39.2 per 100 000 women.[42] The cumulative lifetime risk for women in Hong Kong (to age 75 years) was 1 in 24,[42] compared with 1 in 8 in the US.[43] For a 50-year-old Caucasian woman, the CEAS has estimated a 10% lifetime probability of the development of breast cancer[23] and the estimated median age at which breast cancer develops is 69 years. She also has a 3% lifetime probability of dying of breast cancer. The lower incidence in Hong Kong might make the risk from HRT less than the figures quoted above, but there is no concrete evidence for this. One should also remember the Collaborative Group report, which showed that the increased risk disappeared 4 to 5 years after the cessation of HRT.[37]

Endometrial cancer

An increased risk of endometrial cancer arising from HRT has been reported since the 1970s. The magnitude of the increased risk was reported recently by different groups (Table 3).[23,44,45] Among the 37 studies included in one meta-analysis,[44] the RR for HRT was 2.3 (95% CI, 2.1-2.5) for women who had used HRT. The risk varied with the type of HRT, duration of use, and HRT regimen, and persisted even after the cessation of HRT for more than 5 years. There were more patients with E-HRT than EP-HRT. Higher dosages of conjugated oestrogen were associated with increasing risk. The RRs for 0.3 mg and >1.25 mg were 3.9 (95% CI, 1.6-9.5) and 5.8 (95% CI, 4.5-7.5), respectively. There was no difference between intermittent or continuous regimens. Longer duration of use increased the risk: the RR for less than 5 years' use and more than 10 years' use were 2.8 (95% CI, 2.3-3.5) and 9.5 (95% CI, 7.4-12.3), respectively The risk was less with synthetic oestrogen compared to unopposed conjugated oestrogen, with RR of 1.3 (95% CI, 1.1-1.6) and 2.5 (95% CI, 2.1-2.9), respectively. The risk of death from HRT was not significantly increased (RR=2.7; 95% CI, 0.9-8.0), probably because the cancer risk was greater for non-invasive tumours and tumours of an earlier stage.

Data on EP-HRT were limited and contradictory,[44,45] but suggested that the risk from EP-HRT was lower than the risk from E-HRT. The more days a month that a women was on Progestin, the smaller the endometrial risk from HRT.[45]

For a 50-year-old Caucasian woman, the CEAS[23] estimated a 2.6% lifetime probability of the development of endometrial cancer and an estimated median age at which endometrial cancer develops of 68 years. The annual incidence of endometrial carcinoma is 10 per 100 000 women in Japan, and 100 per 100 000 in the US, with the risk in Europe being about half that of the US.[46] Because endometrial cancer is usually curable, the lifetime probability of dying of endometrial cancer is approximately 0.3%.[23] In women who have used HRT for 10 years, the cumulative excess incidence per 1000 women has been estimated at 42 for E-HRT, and 20 for EP-HRT.[45] In Hong Kong, the age-standardised incidence rate for endometrial

Table 3. Risk of endometrial cancer with hormone replacement therapy

Study	Relative risk (95% CI)	
	Oestrogen*	Oestrogen/progestogen*
Grady et al,[44] 1995	2.30 (2.1-2.5)	0.8 (0.6-1.2)
conjugated oestrogen	2.50 (2.1-2.9)	
synthetic oestrogen	1.30 (1.1-1.6)	
0.3 mg conjugated oestrogen	3.90 (1.6-9.5)	
1.25 mg conjugated oestrogen	5.80 (4.5-7.5)	
<5 years' use	2.80 (2.3-3.5)	
>10 years' use	9.50 (7.4-12.3)	

* For women who have ever used hormone replacement therapy

Table 4. Risk of thromboembolism in current users of hormone replacement therapy

Study	Relative risk (95% CI)	Extra cases due to hormone replacement therapy (per 100 000 women per year)
Daly et al,[47] 1996	3.5 (1.8-7.0)	20
Jick et al,[48] 1996	3.6 (1.6-7.8)	23
Grostein et al,[49] 1996	2.1 (1.4-3.2)	10-20
Gutthann et al,[50] 1997 (pulmonary embolism, women aged 40 to >60 years)	2.1 (1.2-3.8)	4-9
>5 years' use		
Daly et al,[47] 1996	2.1 (0.8-6.1)	
Jick et al,[48] 1996	4.4 (1.6-12.2)	
Grostein et al,[49] 1996	1.1 (0.6-2.1)	
Gutthann et al,[50] 1997 (>1 year of use)	1.1 (0.6-2.1)	
Existing IHD		
Grady et al,[51] 2000	2.7 (1.4-5.0)*	390

* Relative hazard

cancer in 1996 was 7.9 per 100 000, whereas the cumulative lifetime risk of endometrial cancer (to age 75 years) was 1 in 111.[42]

Venous thrombosis and pulmonary embolus

There have been conflicting reports on thromboembolic risk in women taking oestrogen as a contraceptive or replacement therapy.[18-20] Four confirmatory reports have recently been published (Table 4).[47-50] The baseline risk for all thromboembolic events (deep vein thrombosis and pulmonary embolus) in women aged between 45 and 79 years was 10 to 13 per 100 000 per year. After adjusting for risk factors, current users of HRT in these studies had a two- to four-fold increase in thromboembolic risk with HRT, resulting in 10 to 23 extra cases of venous thromboembolism per 100 000 women per year. The risk was increased for current users, but not for past users (HRT stopped 1-6 months previously). The risk was also increased with higher doses of oestrogen,[47,48] and a higher BMI (>25 kg/m^2).[47,48,50] Although the increased risk seemed greatest during the first 6 to 12 months of use,[47,48,50] the effect of HRT for longer than 5 years was not clear. Two reports have shown no significant risk increase with longer than 5 years of HRT (RR=2.1; 95% CI, 0.8-6.1 and RR=1.1; 95% CI, 0.6-2.1),[47,49] whereas one report has shown an increased risk (RR=4.4; 95% CI, 1.6-12.2).[48] There has been no evidence of a significant difference in risk between E-HRT and EP-HRT.[47,48]

The annual baseline risk of pulmonary embolism alone in women aged 50 to 59 years and >59 years was about 6 per 100 000 and 16 per 100 000, respectively.[49] There was a two-fold increase in risk with HRT for current users.[49] Past use, dose of oestrogen, and duration of use were not important for pulmonary embolus. Women in the last study were all registered nurses who participated in the Nurses' Health Study in 11 states in the US, so the incidence of pulmonary embolus may not be directly applicable to the general population.

In women with existing IHD aged between 44 and 79 years (mean age, 67 years), who were given HRT or placebo, the HERS[51] showed a relative hazard of 2.7 (95% CI, 1.4-5.0) with HRT. This group had a baseline risk for all thromboembolic events (deep vein thrombosis and pulmonary embolus) of approximately 230 per 100 000 women per year. The HRT resulted in 390 extra cases per 100 000 women per year. This figure is much higher than those from other reports,[47-49] at least in part due to the different population studied, as well as the fact that the HERS included all thromboembolic events, whether idiopathic or occurring in women with existing predisposing illnesses. Thus, these figures cannot be extrapolated to the general population.

Osteoporosis

Comparing women who have used HRT with women who have never used HRT, the pooled estimate from observational studies of relative risk for hip fracture was 0.75 (95% CI, 0.68-0.84).[23] In healthy women, the multicentre, randomised, double-blinded, placebo-controlled PEPI trial showed that HRT increased bone mineral density (BMD) in the spine and hip, with EP-HRT being especially efffective.[52] There was no significant difference in the number of fractures, but this outcome was measured after a short interval of 3 years.

A cross-sectional study from the University of California, San Diego examined the effect of timing

of HRT on BMD,[53] as measured at the radius, lumbar spine, and hip. Use of HRT increased BMD, but on cessation of treatment, the effect wore off after approximately a decade, even if HRT was started within 2 years of menopause and continued for 10 years. On the other hand, women who received HRT since menopause and those who only started HRT after the age of 60 all had similar increases in BMD.

A more recent multicentre prospective cohort study by the Study of Osteoporotic Fractures Research Group (SOFRG) showed that in women aged 65 years or more without a history of osteoporosis, current users of HRT had lowered risks of fractures at the wrist (RR=0.45; 95% CI, 0.26-0.79), non-spinal sites (RR=0.69; 95% CI, 0.54-0.88), and hip (RR=0.45; 95% CI, 0.2-0.99).[54] The risk reduction was not related to the duration of use (whether more or less than 10 years), except at the wrist, where the risk reduction was greater with a longer duration of use. There was no difference in effect between E-HRT and EP-HRT. The risk was not reduced in previous users of HRT, mirroring the San Diego findings on BMD changes in women who stopped HRT.[53]

In women with a history of osteoporotic spinal fracture, the SOFRG study showed that with HRT, the risk of fracture was reduced at the wrist (RR=0.32; 95% CI, 0.13-0.18) and non-spinal sites (RR=0.63; 95% CI, 0.45-0.89), but not at the hip (RR=0.86; 95% CI, 0.42-1.75).[54] A randomised, placebo-controlled trial from the Mayo Clinic showed that in postmenopausal women aged 47 to 75 years with existing osteoporotic vertebral fracture, the use of transdermal oestrogen lowered the vertebral fracture rate (RR=0.39; 95% CI, 0.16-0.95).[55]

For a 50-year-old Caucasian woman, the CEAS[23] estimated a 15% lifetime probability of having a hip fracture, with a median age at first hip fracture of 79 years. She also has 1.5% probability of dying of a hip fracture. The long-term outcome from trials such as the PEPI trial will hopefully provide more information on the baseline risk and actual risk reduction in osteoporotic fractures in the general population.

History of cancer

In women with hormone-dependent tumours, HRT can potentially increase the relapse rate, although there have been no randomised trials addressing this issue.

For breast cancer, two retrospective analyses published in 1993 suggested that HRT with or without tamoxifen was not associated with adverse effect on the disease.[56,57] In 1996, a retrospective case control study from University of California, Irvine,[58] reported the effect of HRT on survival in women with breast cancer, compared with women with breast cancer who did not receive HRT. Using relative short follow-up intervals of less than 5 years, the study showed that there was no difference in disease-free or overall survival between the two patient groups. In 1997, a retrospective analysis by the University of Texas MD Anderson Cancer Centre[59] on 43 patients who were given oral HRT after the diagnosis of breast cancer showed only one relapse. The median follow-up in that study was 12 years.

For endometrial cancer, one retrospective case control study showed no difference in disease-free or overall survival between patients who did or did not receive HRT,[60] whereas two earlier reports showed that HRT was associated with a increased disease-free survivial.[61,62]

All the above reports are retrospective, with different intervals between diagnosis and the start of HRT and duration of HRT. It is not possible to say for certain at this stage that HRT definitely will not adversely affect disease outcome. The American College of Obstetricians and Gynecologists Committee did not find definite data to support recommendations regarding HRT and endometrial cancer.[63] Whether or not a randomised trial is possible is another matter.

Conclusions and recommendations

Results from well-designed randomised trials are not available for the end-points examined above. The only recent randomised trials are the HERS[31] and PEPI[52] studies, with the former showing no cardiovascular benefit from HRT in women with existing IHD, and the latter showing an increased BMD with HRT. Conclusions from non-randomised studies performed in the 1970s and 1980s do not give a true picture of the real risk or benefit of HRT, because case-control and cohort studies are known to be susceptible to multiple biases.[64,65] Furthermore, errors in recalling data (exposure) can underestimate the association between HRT and the outcome,[66] be it cardiovascular or cancer. Nevertheless, from the available information it would appear reasonable to say that risks for breast and endometrial cancer, as well as thromboembolism, are increased with HRT, but the risks of cardiovascular death and osteoporotic fractures are reduced. The magnitude of the risk to benefit ratio is less certain: it has been reported that despite the increase in cancer, life expectancy may still be longer by 0.7 to 0.8 years,

due to the reduced risk of death from IHD and hip fracture.[23] Extrapolating from the data presented, for every 100 000 women receiving HRT for 3 to 5 years, locally there would be 22 fewer cardiac deaths, 10 to 20 more cases of breast cancer, seven more cases of endometrial cancer, 10 more cases of thromboembolic disease, and slightly fewer cases of osteoporotic fracture. Most of the data and risk estimates, however, were derived predominantly from white Caucasian women, and the study-group baseline risk may also be different.

Ultimately, the decision for or against the use of HRT may be based on exactly which symptom or risk that one is trying to avoid, and on whether the woman has an increased baseline risk for the various end-points discussed above. If local menopausal symptoms can be controlled by local treatment, then systemic treatment will not be necessary. If menopausal symptoms warrant HRT, a few years of treatment may be sufficient and will not excessively or persistently increase the other risks mentioned above, except for endometrial cancer—and even that may be circumvented by the use of EP-HRT.

If cardiovascular risk is the main concern, there is only observational evidence of HRT being useful in women without existing IHD. Early results in those with IHD have shown no risk reduction. Until results from randomised trials are available, it would seem better to reduce this risk with changes in lifestyle such as exercise, healthy diet, and cessation of smoking, particularly if the population baseline risk is low.

If osteoporotic fracture is the main concern, the approach for women without a history of osteoporotic fracture may be to start HRT at around 60 years of age, because the effect on BMD with this approach is similar to starting HRT at menopause.[53] For younger women with a history of osteoporotic fracture, HRT does not reduce the risk of hip fracture, which is the main cause of morbidity. In this respect, the selective oestrogen receptor modulator, raloxifene,[67] gives similar results, with a reduction in vertebral but not hip fractures (RR=0.7; 95% CI, 0.5-0.8). The risk of thromboembolism was also increased (RR=3.1; 95% CI, 1.5-6.2). A longer follow-up from this study may shed more light on this. Alternatively, the use of alendronic acid in women with osteoporosis has been shown to reduce fractures by 36% (relative hazard=0.64; 95% CI, 0.50-0.82) without cardiac or uterine side effects.[68] This would make it a logical choice, if osteoporotic fracture is the only issue to be addressed.

For women with previous thromboembolism, it would be prudent not to give HRT. This group of women have an increased baseline risk already, and HRT would almost triple the risk to almost 0.6% per year. For the general population, the risk is exceedingly low (<0.03% annual risk) and probably should not be a factor in deciding for or against HRT.

For women with a history of cancer, there is no hard evidence on which to base a treatment policy. The risk of cancer or its exacerbation, however small that risk may be, could be sufficient to prevent them from using HRT, especially in the absence of firm, randomised data on its efficacy.

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