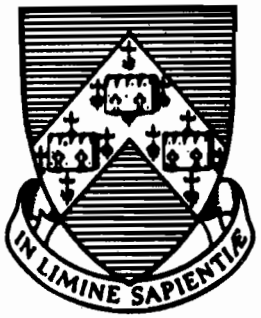

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The Cost Effectiveness of Hormone Replacement Therapy: A Review

by Maria Goddard

DISCUSSION PAPER 73

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Abstract

The use of postmenopausal hormone replacement therapy (HRT) has received much attention both in the medical and lay press in recent years. There is considerable pressure to extend the use of HRT both as a method for relieving the distressing symptoms of menopause and also as a prophylactic measure to prevent osteoporosis and subsequent bone fractures in high risk women.

This paper critically reviews the available evidence on the risks and benefits of HRT use, focussing in particular on symptom relief, osteoporosis, breast cancer, endometrial cancer and heart disease. It goes on to consider whether the use of HRT is cost effective in terms of the resources used in the provision of the therapy and the possible resource effects associated with the risks and benefits outlined above.

Finally, whilst concluding that on balance some forms of HRT for certain women do indeed appear to be cost-effective on the basis of available evidence, there are several major gaps in the information required to make firm conclusions. These are outlined, and priorities for future work are indicated.

The report is organised as follows:

The above section is sub divided as follows:

The Cost Effectiveness of Hormone Replacement Therapy

(1) Introduction

The use of postmenopausal hormone replacement therapy (HRT) has increasingly become a focus of attention for the medical and lay press in recent years, but it is still the case that far fewer women in the UK are given HRT when compared with North America and other European countries (Belchetz, 1989; Spector, 1989). Although it has been suggested that this is due to the "innately conservative" medical professional (Belchetz, 1989; p. 1467), it is certainly the case that much confusion and uncertainty regarding the relative risks and benefits conferred by HRT exists and this is likely to strongly influence prescribing decisions.

The major health benefits arising from the use of postmenopausal HRT are the relief of very disruptive menopausal symptoms, in particular vasomotor symptoms (flushes and sweats), potential protection from osteoporosis and thus subsequent bone fractures and lastly, a protective effect on morbidity and mortality from cardiovascular disease. On the contrary, the drawbacks associated with HRT use include the elevated risk of endometrial cancer in women with an intact uterus (although this was mainly a concern in the past, when unopposed oestrogens were prescribed) and a possible increased risk of breast cancer. The evidence relating to these issues is reviewed later in this paper, but it is apparent that the use and prescription of HRT always

involves the weighing-up and balancing of the associated risks and benefits.

Indeed, a recent survey of over 3,000 long-term users of HRT in the UK found that patient initiated demand was the most frequently mentioned first reason given by women as reason for prescription by their doctors and almost half the sample identified the mass media or personal contact as being their first source of information about HRT (Hunt, 1988). However, it is also the case that, despite high expectations from HRT, many women (at least in the USA) do not comply fully with therapy or even fill their prescriptions, which is mainly due to confusion and fear about the relative risks and benefits associated with HRT (Ravnikar, 1987). Less than 10% of postmenopausal women in the UK use HRT at present and this is despite the fact that after the mid-1970s, the prophylactic role of HRT in the prevention of osteoporosis was recognised and the use of HRT became more widespread than had previously been the case. Prescriptions for HRT peaked in the UK around the late 1970s, but then deteriorated for a few years in response to the particular concern of the elevated risk of endometrial cancer in users of unopposed oestrogens (Hunt and Vessay, 1987). However, the addition of progestogen for women with an intact uterus reduces this risk and the issue of prescriptions for opposed therapy has subsequently increased.

A recent survey of menopausal women and women who had undergone hysterectomy or oophorectomy in three general practices in London, showed that only 10% of over 3000 respondents had ever received HRT (18% of postmenopausal respondents) and, moreover, the mean duration of use was very short (Spector, 1989). Of more importance was the fact that 70% of the "high risk" women (i.e. those with bilateral oophorectomy) and 75% of "medium risk" women (hysterectomy) had never received HRT, despite the elevated risks of

osteoporosis and heart disease faced by these particular groups of women. The author reports that such women had no medical contraindications to therapy (but it is unclear how much information was obtained about the extent of contraindications) and thus should have generally been prescribed HRT.

In addition to consideration of the relative benefits to health, the introduction of widespread use of HRT by a substantial proportion of the ten million postmenopausal women in the UK would obviously have a considerable economic impact on NHS resources, and this has also been the focus of discussion recently (for example, Griffen, 1990, p.43). It is evident that the additional costs of the extension of HRT use to more women in the UK may be completely or partially offset by a reduction in the resources used for the treatment and care of osteoporotic fractures and cardiovascular disease. However, these must also be offset against any increases in resources needed to treat women developing endometrial[1] or breast cancer as a consequence of HRT use.

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(1) This is not, however, likely to be an issue in the UK with the prescription of combined HRT for those women with an intact uterus.

(2) General Background Information

In general it is accepted that unopposed oestrogens (ORT) should be given only to women without a uterus or to those who are totally progestogen intolerant (as long as careful monitoring is continued even into post-treatment phase); whilst for those with an intact uterus, progestogen should be added for part of the cycle (HRT), in doses large enough to provide protection against endometrial cancer, but not to produce deleterious effects on blood lipids (Whitehead and Lobo, 1988; British Gynaecological Cancer Group, 1981). The duration of use depends upon the aim of treatment: short-term use of approximately 1-2 years is usually sufficient to deal with vasomotor symptoms; but longer use of up to ten years has been suggested for the prophylaxis of osteoporosis (Consensus development conference, 1987; Drife, 1989).

There are four major routes of administration of HRT, the most commonly used is the oral route and often takes the form of conjugated oestrogens or oestradiol valerate (the use of ethinyl oestradiol has declined over the last decade; Stevenson and Whitehead, 1990). The addition of oral progestogen can be incorporated for between 10-12 days in each cycle.

Secondly, oestrogen implants are also available and last approximately 4-8 months when they are then renewed if needed. These obviously solve the problem of compliance and in theory they should minimise gastrointestinal side-effects and adverse hepatic effects.

Thirdly, the use of oestrogen creams applied via the vagina should in theory also avoid any adverse hepatic effects, but studies have shown that as they are absorbed into the circulation, they still do exert a deleterious impact on the liver (Judd, 1987).

Lastly, oestradiol patches applied to the skin every three to four days have recently been introduced in the UK. Such patches release oestrogen transdermally and again should have the same hepatic advantages as implants. Research in the US has suggested that this is the case (Judd, 1987) and also that the patch is well-tolerated, effective in terms of reducing hot flushes and likely to be associated with high compliance levels (Utian, 1987; Ravnikar, 1987). This however must be tempered by the fact that the patch may cause skin rashes, or indeed, become detached from the skin during use. Longer term experience with this system will isolate the incidence of such possible drawbacks.

The effect on lipid levels (and thus heart disease) and on skeletal integrity has been less well researched due to the relative novelty of this method, but a recent study of 16 users of transdermal HRT concluded that the addition of a <u>non-oral</u> progestogen (i.e. transdermal) to oestrogen does not adversely affect the favourable oestrogen - induced changes in lipid levels (Whitehead et al., 1990). The overall effects are likely to depend upon dose and duration as well as route of administration (Lancet editorial, 1988; Stampfer and Sacks, 1988).

(3) Menopausal Symptoms

The main aim of short-term HRT use is to relieve the symptoms associated with the onset of the menopause. Major symptoms include hot flushes, night sweats, vaginal dryness, depression, anxiety, memory loss, sleeplessness and nervousness, and whilst these are obviously not life threatening conditions, they certainly affect adversely the quality of life of the postmenopausal woman. Moreover, the view that such symptoms are relatively mild and short-lived is being challenged (Belchetz, 1989).

Indeed, surveys show that symptoms such as sweating, flushes, difficulty with decision making and loss of confidence, peak in women at the age of menopause (Bungay et al., 1980) and the incidence of hot flush episodes can reach 85% in menopausal women, continuing up to 5-20 years after the onset of the menopause (Rebar and Spitzer, 1987; Mulley and Mitchell, 1976). Some studies have shown that about one-third of women experiencing hot flushes, classify them as severe (Rebar and Spitzer, 1987).

It is generally agreed that vasomotor symptoms are directly linked to the menopause and to declining oestrogen levels, whilst there is more debate about whether or not psychological symptoms such as depression can also be ascribed directly to oestrogen deficiency. Nevertheless, the use of oestrogen for the relief of all types of menopausal symptoms has been studied widely. In the U.K., a double-blind, placebo-controlled trial was undertaken to assess the effect of conjugated oestrogens on the menopausal symptoms experienced by 30 patients presenting with symptoms at a group practice (Coope et al., 1975). Women were randomly allocated to three months placebo treatment followed by

three months hormone treatment, or vice versa. A range of symptoms were scored according to severity. Assessments were made at baseline and at monthly intervals, and were weighted to form a "menopausal index". A large improvement, as measured by changes in the index, was produced by both the placebo and the oestrogen in the first three months, but the difference between groups was not significant. However, those who received oestrogen first, did not show a placebo response in the second three months, whilst those in the other group did show a small, but significant further improvement on switching to oestrogen.

Various symptoms were also considered separately, and in the first three months, oestrogen was significantly better at reducing the number of hot flushes than placebo. Thus, although a definite placebo response was noted, oestrogen did appear to fare better with respect to its effectiveness in reducing or abolishing hot flushes.

Other studies have tended to support this general finding, when hot flushes are measured either subjectively by patients' perceptions, or objectively by temperature (Campbell and Whitehead, 1977; Tataryn et al., 1981; Dennerstein et al., 1978). A survey of over 3,000 women receiving HRT in the U.K., found that overall, 89% thought the therapy had helped and over 70% of these claimed that the therapy had helped in relation to hot flushes (Hunt, 1988).

However, although there seems to be considerable evidence that HRT is very effective in dealing with vasomotor symptoms, the evidence regarding its effect on psychological symptoms is less conclusive. Whilst it has been argued that as oestrogen can prevent flushes and sweats, it can also reduce

anxiety and depression via a mediating effect on sleeplessness (Rebar and Spitzer, 1987), some research has failed to confirm this. For instance, in a double-blind, placebo-controlled crossover study of 55 depressed menopausal women, there was no statistically significant difference in the improvement in the Beck depression inventory score between groups taking oestrogen and those taking the placebo (Coope, 1981). In addition, there was no difference between groups in the number of consultations or prescriptions for psychoactive drugs (although again, in this trial, oestrogen was effective in controlling vasomotor symptoms).

Early research concerning the effect of HRT on psychological symptoms has been summarised by Dennerstein and Burrows (1978) and they conclude that whilst, ".. administration of oestrogens alone or in combination with progestogens appear to alleviate some of the symptoms, more detailed research is needed into the relationship between psychological symptoms and the menopause" (p.55). In particular, the methodology of many of the early studies has been criticised, and the issue of whether some of the positive findings on depression levels were due to the intervening impact on sleep via the reduction in vasomotor symptoms, has also been debated.

A more recent study undertaken in the U.K. considered the effects of oestrogen, oestrogen and testosterone combined, or placebo[2] (all in implant form) on the psychological symptoms of 70 women with menopausal symptoms (Montgomery et al., 1987). Again, the design was double-blind, but patients remained in their assigned group after randomisation and were assessed at bi-monthly intervals using standard psychiatric scaling methods. For post-

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(2) A progestogen was added for those with an intact uterus.

menopausal women, symptoms showed a significant improvement in all groups, but after a period of four months, there was no significant difference between groups.

The large U.K. survey of HRT users (Hunt, 1988) also found that much smaller proportions of women claimed that therapy was beneficial for depressions, anxiety and tension, than was the case for vasomotor symptoms.

In conclusion, although further research may be necessary before the precise aetiological role of HRT in the alleviation of psychological symptoms is clarified, it is apparent that it has a vital role in the amelioration of vasomotor and other very disruptive symptoms experienced by post-menopausal women.

(4) Osteoporosis

Prevention of osteoporosis is the major reason for continuing HRT for menopausal women into the long run. Short term use of HRT is sufficient to alleviate most menopausal symptoms, but evidence that oestrogen (with the addition of progestogen to prevent deleterious side effects of endometrial cancer in those women with an intact uterus) can prevent or delay the development of postmenopausal osteoporosis was a powerful reason for the move in the mid-70s towards more extended use of HRT in such women.

The onset of menopause is accompanied by a reduction in oestrogen levels, and in many women (but not all), this can lead to thinning of the bones, making them more fragile and subsequently causing a higher risk of experiencing bone fracture, particularly of the wrist, hip and spine. Whilst natural menopause is accompanied by a gradual fall in oestrogen levels, the loss is most striking and rapid in those undergoing premature oophorectomy (Stevenson and Whitehead, 1982). Whilst HRT acts to prevent the loss of bone, if it is to be considered as a prophylactic for osteoporosis, then it is essential that it can affect the subsequent fracture rate rather than merely having an impact on the technical measure of bone mass or density. It is the occurrence of fractures due to osteoporosis that is the cause of morbidity and indeed mortality in such women; the presence of osteoporosis does not itself cause symptoms. This important link is considered later in more detail.

It is evident that the problem of osteoporosis is widespread. It has been estimated that it will affect 25% of women in Great Britain by the time they are 60, and 50% of 70 year olds (Bryan, 1989). As the number of hip

fractures has risen rapidly in recent years, to an annual rate of about 37,500 in England and Wales (Drug and Therapeutics Bulletin, 1989), the associated morbidity and mortality (plus the subsequent costs of treatment and care) of osteoporotic hip fractures is likely to be substantial. Evidence from the UK suggests that the increase in the incidence of hip fracture has almost doubled for females aged 75+ over a period of 10 years, a rate which is in excess of the rate of growth in the elderly population (Wallace, 1983). As at least half of those able to walk before sustaining a hip fracture cannot walk independently afterwards, it is evident that loss of mobility and thus independence, will often precipitate admission to long-stay institutional care (Griffen, 1990). The mortality and morbidity effects of vertebral and wrist fractures, although important, are likely to be less significant than hip fractures.

Several early studies have examined the relationship between bone mass and oestrogen use, for example, Lindsay et al. (1976), Horsman et al., (1977) and Nachtigall et al. (1979). Indeed, such studies have been able to give an insight into when treatment is likely to be most effective and how long the effects of treatment will continue after use is terminated. For example, Nachtigall et al. (1979) found in their 10 year prospective trial of 84 pairs of matched post-menopausal patients, that therapy (high dose oestrogen plus progestogen) was most effective at reducing bone loss if delivered within 3 years of the onset of menopause. It is generally accepted that treatment should begin as soon after menopause as possible (Belchetz, 1989; Consensus Development Conference, 1987). The optimum duration of treatment is generally agreed to be about 10 years, but there is conflicting evidence regarding the duration of the beneficial impact on bone loss when treatment ends. For example, whilst some authors are doubtful whether any protective effect

persists at all after use has ceased for several years (Kelsey and Hoffman, 1987); others point out that subsequent bone loss resumes at a normal rate and thus has a continued protective effect as it would, in practice, delay the onset of fractures until close to the end of expected life span (Christiansen et al., 1981).

Later studies have also shown that bone loss can be prevented by oestrogen therapy (e.g. Gotfredson et al., 1986) and some have aimed to overcome the problems associated with accurately measuring bone-loss and density to detect osteoporosis (Heath, 1988) by using high precision equipment (Munk-Jensen et al., 1988). This latter study examined the extent of vertebral and forearm bone loss in early postmenopausal women before and after continuous or sequential treatment with combined oestrogen and progestogen in a double blind placebo controlled trial. Those women who received HRT experienced statistically significant reversals in the extent of vertebral bone loss (i.e. they gained bone mass) when compared with the placebo group. The same finding was true for the loss of bone from the distal forearm, but this effect was less pronounced.

Similarly, a double-blind controlled study of the effect of calcium (also proposed as a possible prophylactic therapy for osteoporosis) versus combined oestrogen and progestogen versus placebo for preventing bone loss in postmenopausal women found the HRT to significantly affect bone mineral content (Riis et al., 1987). Both the calcium and placebo groups showed a significant decrease in the bone mineral content (measured with four different methods); whereas the values remained unchanged over a two year period for the HRT group.

However, as mentioned previously, it is obvious that of most importance is the impact of reversing or delaying bone loss upon the morbidity and mortality caused by subsequent fractures, especially of the hip. Once more, many studies have addressed this topic, but it is an inherently difficult area, as whereas HRT can feasibly affect the rate of bone loss within two years of use, the subsequent effect on the incidence of fractures would not become evident for many years. This is particularly true for hip fractures which tend to occur mostly in the 75+ age group. It is obvious then that prospective studies which allow sufficient follow-up to detect such an effect would not be practical. For these reasons, the majority of studies investigating the link between osteoporosis, fractures and HRT tend to be either case control studies or retrospective cohort studies.

Case control studies generally look at the prevalence of exposure to oestrogen in women with fractures, compared with the prevalence in women without fractures, the implication being that a lack of association between oestrogen use and fractures represent a protective effect. Ettinger et al. (1985) reviewed the five published case control studies which found a negative association between oestrogen use and fractures of wrist and hip and concludes that they are all flawed in some way (Weiss et al., 1980; Hutchinson et al., 1979; Paganini-Hill et al., 1981; Johnson and Specht, 1981; Kreiger et al., 1982). In particular, the problems of limiting the study to the "low risk" group (i.e. under 75 year olds) and accepting brief oestrogen exposure as a discriminator are widespread. However, in general, the studies have shown that the risk of hip fracture and distal radius fracture may be reduced by 50% or more if oestrogens are used over five years or more.

Ettinger et al. attempt to overcome some of the difficulties of gaining significant results for hip fractures (due to long length of follow-up needed as fractures occur in older age groups) by pooling the data from the five case-control studies mentioned earlier. This yielded a total of 590 hip fractures and 2021 controls, with an average age of 70 years. The combined risk ratio for long term oestrogen exposure (3-5 years of use) in persons with fracture as compared to that of controls was 0.4 (95% confidence limits of 0.2 to 0.5). This therefore accords well with the general results of the 50% reduction found in the earlier studies. Ettinger's own study however, which was a retrospective analysis of 245 oestrogen users matched with 245 case controls, with an average follow up of 17.6 years, did not find differences in the incidence of hip fracture. The results of the analysis on the pooled data, led the authors to suggest that this was likely to be due to the low incidence of hip fractures, their small sample size and an inadequate follow up period.

Retrospective analysis, can, to some extent, avoid some of the design problems outlined earlier and again, Ettinger has looked critically at the major studies undertaken. For example, the study by Hammond et al. (1979) found a statistically significant difference in the prevalence of all fractures between users and non-users, but it is noted that no information was provided on specific fracture types and that the controls differed significantly from the oestrogen group in important ways. In particular, the oestrogen users were thinner than the controls, and as thinness is one of the "risk factors" for fractures and osteoporosis, this can seriously affect the validity of the results.

Ettinger's study focused on those who had used oestrogen for at least five years and found that osteoporotic fracture was over 50% lower in the user group, giving a relative risk ratio of 2.2 for controls (95% confidence limits 1.5-3.8). Although wrist fractures were fewer in the user group, only the differences in vertebral fracture reached statistical significance (relative risk for non-users - 2.7; confidence limits 1-8.1).

Two U.K. studies addressed the issue of osteoporosis and hip fractures. A study by Aitken (1984) looked at all women with fractures of proximal femur in one district over a 12 month period, recording details of the injury and bone mass measurements. The study showed that falls were the major cause of fracture in this series of women. This is of importance in considering the role of oestrogen in the prevention of fracture, as if trauma is the major cause, then oestrogen would have a more limited role to play via the prevention of osteoporosis (Heath, 1988). Generalised osteoporosis was found to influence the type of fracture sustained rather than being a prerequisite for fracture. Moreover, 16% of fractures occurred in women with no evidence of osteoporosis. However, the author does note that the method of assessing osteoporosis was confined to detection of general rather than localised osteoporosis which might obscure the true incidence of this illness. Although they point to the evidence from postmortem studies of a good correlation between mass at other sites and at the metacarpal midshaft, this is obviously an important element in the interpretation of the results.

A later study undertaken in the U.K. by Cooper et al (1987), looked at 708 elderly people who had fallen and injured a hip, in order to detect the relative importance of osteoporosis. They concluded that below 75 years of

age there was indeed a steep (and statistically significant) increase in the relative risk of fracture with reduced bone mass. However, it was found to be less important in the 75+ age group.

In the US, a review of 15 case-control studies which investigated the link between osteoporosis and risk of hip fracture has shown that the well-designed studies generally find a smaller difference in the extent of osteoporosis between controls and cases than less rigorously designed studies. (Cummings, 1985). Similarly, it has been suggested that although osteoporosis seems to be a necessary condition in the cause of fracture, it is not sufficient and other causes such as immobility should be considered in conjunction with osteoporosis (Melton et al., 1986). The role of factors such as diet, alcohol use, smoking and certain medications have also been recently reviewed (Griffen, 1990).

The large Framingham Heart Study, undertaken in the USA, attempts to overcome some of the difficulties associated with demonstrating the effect of oestrogen use on <u>hip</u> fracture (Kiel et al., 1987). Rather than relying upon case control studies with the associated problems outlined earlier, the authors undertook a retrospective cohort study with a follow up period of more than 20 years, allowing for the long latency period between menopause and the occurrence of hip fracture. The study used evidence collected on 2873 women at biennial examination and examined the incidence of hip fractures amongst those who had used oestrogens at any time and those who had used them within the previous two years (recent users). After adjusting for age and body weight (which were both strongly associated with hip fracture), it was found that <u>any</u> postmenopausal use of oestrogen conferred a 35% reduction in the risk of hip fracture in the following two years (relative risk compared with non

users - 0.65; confidence limits = 0.44 - 0.98). This was further subdivided to show that whilst oestrogen use in the past was less protective (relative risk - 0.74; confidence limits - 0.49, 1.14); for recent users, a 66% reduction in the risk of hip fracture was noted (relative risk - 0.34; confidence limits = 0.12 - 0.98). Moreover, the study results do suggest that there may well be protective effects from administering oestrogens to older women (age 65+) although this is not a definitive conclusion and would need further studies to support or refute it.

Although it has been noted that such a large protective effect even after only two years exposure to oestrogens is surprising (Heath, 1988), the authors themselves remark that if it seems unlikely that such short use could affect bone loss, a possible explanation is that the oestrogen therapy is protecting from fractures via another route. The results of this study should be taken seriously as it is the largest cohort study undertaken and overcomes many of the biases likely to be present in other studies, whether case-control or cohort. In particular, as the authors note, they were able to include those women who had died as a result of their hip fractures, whereas other earlier case-control studies include only survivors of fractures.

Additionally, as women were asked repeatedly about oestrogen use at each examination, problems of inaccurate recall were minimised. Lastly, the mean age at first fracture was 75 (+/-9) years, occurring, on average, 30 (+/-11) years after the menopause. The inclusion of older women in this study thus minimises the chances of missing the substantial numbers of fractures occurring long after the menopause and oestrogen use begins. The only drawback of course is that oestrogen use has been offered to some of the women in the study, presumably as they were at high risk of developing osteoporosis

in the first place and thus the study may produce biased results. However, the possibility of this has been reduced to some extent as the authors corrected not only for age and weight, but also other confounding factors which did not alter the risk ratios substantially.

Due to the possibility of side effects of unopposed oestrogen (ORT) and also of combined HRT (discussed in other sections), it has often been proposed that in order for HRT to be most cost-effective in prevention of osteoporosis, it should be confined (as a prophylactic therapy) to those at "high risk" of developing osteoporosis, rather than prescribed for menopausal women in general (Heath, 1988; Consensus Development Conference, 1987; Riggs and Melton, 1986). It has been noted that historical risk factors could be used, although it has not yet been possible to weight them according to their relative importance. The following major risk factors have been put forward by Riggs and Melton who also distinguish between what they term "Type I" osteoporosis associated with accelerated bone loss and post menopausal status, and "Type II" affecting men and women at an older age with no accelerated bone loss:-

<u>Major Risk Factors for Type I Osteoporosis in Women</u>

Postmenopausal

White or Asian

Early menopause

Positive Family History

Short Stature and Small Bones

Leanness

Low Calcium Intake

Inactivity

Nulliparity

Gastric or Small Bowel Resection

Long term Glucocorticoid therapy

Long-term use of Anticonvulsants

Hyperparathyroidism

Thyrotoxicosis

Smoking

Heavy Alcohol Use

Others have added to this list additional risk factors, such as lactose or milk intolerance (indicating possible calcium deficiency), excessive exercising and medical conditions such as renal disease, diabetes and long term rheumatoid arthritis.

A recent study undertaken in Denmark claims that a single blood sample and urine sample plus measurement of height and weight yields enough information to correctly identity 79% of "fast" bone losers and 78% of "slow" bone losers (Christiansen et al, 1987). This implies that there might be a relatively simple method of identifying the 'high risk' section without undertaking more extensive and expensive bone screening methods developing in the United States and also recently in the UK.

In conclusion the links between oestrogen use and prevention of osteoporosis, and between osteoporosis and risk of fracture and subsequent morbidity and mortality, are quite clear (especially for hip fracture) - what is less clear is the duration of therapy needed to produce such protective effects and the magnitude of the other risks associated with long-term HRT

use. The effects of HRT use on various aspects of women's health is the subject of the following sections.

(5) Breast Cancer

This is probably one of the most controversial aspects of HRT, as there appears to be no consensus about the existence or magnitude of any increased risk of developing breast cancer in women receiving HRT.

A priori, there are reasons why HRT might play a role in breast cancer, as epidemiological studies have provided evidence of the role of ovarian hormones in the aetiology of breast cancer, showing that early menopause has a protective effect for women. Accordingly, prolonged exposure to such hormones through the administration of HRT (or indeed through a delayed natural menopause) is likely to increase the risk of developing this disease. Some evidence regarding the risks associated with use of combined oral contraceptives (COC) suggest that there is no indication of increased risks of breast cancer for users of COC (Lancet Editorial, 1986, Henderson et al., 1988a). However, for those taking COCs at an early age and also later on in life, around the time of the menopause, it does seem likely that some increased risk may be associated with COC use for some groups (Brinton, 1982; Vessey et al., 1979; Henderson et al., 1988b).

One of the major problems in detecting increased risk due to HRT use again lies in the long latency period for the development of beast cancer necessitating a long follow up period for cohort studies. For this reason, the majority of research in this area has focused on the use of case-control studies for the investigation of the link between HRT and breast cancer.

The quality of the studies varies enormously but Table 1 summarises the main design and methodological features of the more recent studies and also the results which are usually expressed in terms of the 'relative risk' (RR) of developing breast cancer for the hormone user group compared with a non-user group drawn from the population controls.

It is evident that many studies have found an elevated risk of developing breast cancer when comparing users of hormones (mainly conjugated oestrogens (ORT), unless otherwise stated in the table) with non-users. The relative risks reported for study subjects overall, range from 0.7 (i.e. a reduced risk) to 1.59. However, although this type of range is widely quoted in the literature, it is important to note that in only two cases do the elevated relative risks for ever use reported for women in general, reach levels of statistical significance (i.e. differ significantly from 1.0). The table shows that the relevant studies by Hoover et al. (1981) and Hunt et al. (1987) give RR of 1.4 and 1.59 for ever-use.

Indeed, the general picture of a possible modest increase of breast cancer risk is further complicated by findings suggesting the opposite is true. In particular, the study undertaken by Gambrell et al. (1983) actually produced the opposite results, indicating that those who were <u>not</u> undertaking therapy had a higher risk of breast cancer than those receiving either oestrogen alone (ORT) or oestrogen and progestogen combined (HRT). The details of this study are discussed in the next section as the major focus was on the apparent protective effect of <u>combined</u> HRT. However, the results have been criticised, mainly because of the small number of cases involved in some of the sub-groups analysed and, more importantly, because of the possibility of bias in the results due to failure to adjust for potential differences

Table 1: Recent Studies of HRT and Breast Cancer

AUTHOR(S)	DATE	SIZE OF STUDY		DURATION OR DOSAGE OF HRT	RELATIVE RISK (where 'no use' = 1.0)			COMMENTS ON DESIGN/RESULTS
		CASES	CONTROLS		OVERALL	AT LEAST ONE INTACT OVARY	NO OVARIES	
Ross et al	1980	138	281	Ever use 1-1499 TMD 1500 + TMD	1.1 0.8 1.9	1.4 0.9 2.5*	0.8 0.9 0.7	RR adjusted for possible confounders except for last group where numbers too small. 3 sources of data on use were available.
Hoover et al	1981	345	611	Ever ≤ 4 years 5 + years ≥ 1.25 mg	1.4* 1.4 1.7* 1.8*	1.5 - - -	1.3 - - -	Results not altered by adjusting for certain factors. Some patients premenopausal.
Hulka et al	1982	199	451 hospital 852 community			Hospital Community		Two sets of controls used: hospital and community RR adjusted for age, race and history of gall-bladder disease. Unadjusted for those undergoing surgical menopause. 'No use' includes those using for < 6m.
				Ever	-	1.8 1.7	1.3 1.2	
				6m - 3 years	-	2.1 2.6	-	
				4-9 years	-	1.5 1.6	-	
				10 + years	-	1.7 0.7	-	
				≤ 0.625 mg	-	1.9 0.8	-	
				> 0.625 mg	-	1.0 0.8	-	
Gambrell et al	1983	53	Survey rates	Oestrogens Oestrogen & progestogen Untreated	0.7 0.3* 1.4*	- - -	- - -	Possible bias in results due to design.
Kaufman et al	1984	1610	1606			Natural Hysterectomy		Results refer to conjugated oestrogens, study reports for other types also. RR adjusted for other factors. Results reported for both natural menopause and hysterectomy (with at least one ovary intact)
				Ever	0.9	- -	0.7	
				< 1 year	-	0.9 1.3	0.4	
				1-4 years	-	0.9 1.2	0.8	
				5-9 years	-	0.7 0.7	1.1	
				≥ 10 years	-	1.3 0.3	0.5	
				< 1.25 mg	-	1.2 0.7	2.0	
				≥ 1.25 mg	-	0.7 0.4	0.5	
Hiatt et al	1984	119	119	Ever ≥ 3 years	- -	- -	0.7 1.8	All subjects had bilateral oophorectomy.
Nomura et al	1986	341	340	Ever	(a) 0.9 (b) 1.1	- -	- -	(a) refers to Caucasian subjects (b) refers to Japanese subjects.
				< 1 year	0.9 2.4*	-	-	
				1-5 years	0.7 0.7			
				6+ years	1.3 1.9			
Brinton et al	1986	1960	2258			Natural Surgical		(a) 15-19 years. Adjustment for possible confounding factors did not change RR. Results for natural and surgical menopause (at least one ovary retained) are presented.
				Ever	1.03	1.05 1.01	1.14	
				< 5 years	0.89	0.95 0.82	0.98	
				5-9 years	1.09	1.05 1.15	1.18	
				10-14 years	1.28	1.30 1.16	1.64	
				15+ years	1.24(a)	1.70* 1.26	1.43	
				20+ years	1.47*	- -	-	

Table 1: Recent Studies of HRT and Breast Cancer (Continued)

AUTHOR(S)	DATE	SIZE OF STUDY		DURATION OR DOSAGE OF HRT	RELATIVE RISK (where 'no use' = 1.0)			COMMENTS ON DESIGN/RESULTS
		CASES	CONTROLS		OVERALL	AT LEAST ONE INTACT OVARY	NO OVARIES	
Buring et al	1987	221	Survey rates			Natural Surgical		RR adjusted for age, not altered by other factors. Results for natural and surgical menopause (at least are ovary retained) are presented.
				Ever	1.1	1.1 1.0	1.1	
				< 5 years	1.0	1.1 1.0	0.9	
				5+ years	1.3	1.3 1.4	1.3	
Wingo et al	1987	1369	1645			Natural Surgical		Authors also give results for intermediate years. (a) ⩾ 5 years. (b) ⩾ 15 years. 'Use' includes those with 3+ consecutive months of use.
				Ever	1.0	0.8 1.1	1.3	
				10-14 years	0.8	0.7(a) 0.6	1.5	
				⩾ 20 years	1.3	- 2.0(b)	1.7(b)	
Hunt et al	1987	50	Cancer Registry Rates	Ever	1.59*	2 ovaries 1 ovary 1.19 3.08*	1.66	'Use' includes those with more than 1 year of use British study - cohort plus case-control analysis
Bergkvist et al	1989	253	Regional Rates	i. Oestrogen in any form				Cohort plus case-control analysis. 6% premenopausal. 'No use' may include some short term users.
				Ever	1.1	-	-	
				3-6 years	1.3			
				⩾ 9 years	1.7*			
				ii. Oestrogen only				Full data available on 196 out of 253.
				< 6 m	0.8	-	-	
				⩾9 years	1.8*			
				iii. Combination				
				< 6 m	0.5	-	-	
				6.9 years	4.4			
				iv. Conjugated oestrogen				
				Ever	1.1			
				< 6 m	1.5			
				⩾6 years	1.3			

* Indicates risk significantly different from 1.0 at 5% level or trend significant at this level.

amongst women in different treatment groups (Ernster and Cummings, 1986). In particular, women with a strong history of family breast cancer would be less likely to receive therapy and the authors did not provide data on this aspect of medical history for each group as a whole, only for breast cancer cases within each group.

Similarly, an additional analysis of the prognosis and mortality associated with breast cancer in different sub-groups has been undertaken (Gambrell, 1984) and suggests that women with breast cancer who were taking hormones had lower mortality rates than those women who developed breast cancer and were not receiving therapy.

However, once more, there are methodological flaws in this analysis, including the failure to examine breast cancer mortality specifically, rather than overall mortality. As the untreated group were followed up for longer and were older at diagnosis, then it is unsurprising that they had a higher mortality rate than those in the treatment groups. Whilst this does suggest that there may well be an elevated risk for those women taking HRT, analysis of the relationships within particular sub-groups is perhaps even more important. The results can be analysed according to ovarian status of the women, the type of therapy administered and the duration or dose of treatment.

1. Ovarian/Uterine Status

Women who have undergone a bilateral oophorectomy have been found to have a lower risk of breast cancer than those women having a natural menopause (intact uterus) or a hysterectomy (leaving at least one ovary intact) (Bergkvist et al., 1988). Thus, even if HRT increased the risk of breast

cancer, women with no ovaries may not experience an elevated risk relative to non-users in general. This was the case in Hulka's study where the protective effect of oophorectomy was maintained irrespective of oestrogen use (Hulka et al., 1982). However, the study undertaken by Brinton showed that whereas this sub-group of women indeed had a lower risk of breast cancer, this was eliminated by oestrogen use, bringing the risk for those with no ovaries to the same level as women with a natural menopause (Brinton et al., 1986). This interaction may account in part for some of the contradictory results in the above table.

Hunt et al. (1987) found an equally complicated relationship between ovarian and uterine status and breast cancer risk in their cohort study. Their results are summarised in the table below.

Number of Cases

	O[1]	E[2]	O/E[3]	95% CI
Uterus intact	24	20.18	1.19	(1.18-2.10)
Hysterectomy with bilateral oophorectomy	10	6.01	1.66	(0.80-3.06)
Hysterectomy with at least 1 ovary intact	16	5.19	3.08	(1.76-5.01)
Total	50	31.38	1.59	(1.18-2.10)

Source: Hunt et al., 1987.

(1) Observed cases.
(2) Expected cases.
(3) Ratio of (1)/(2).

The risk ratio was therefore highest for those women who had undergone a hysterectomy but still had at least one ovary, and lowest for those with an intact uterus. The authors conclude that this is difficult to interpret in the light of the protective effect of bilateral oophorectomy. Despite further detailed analysis of the issue, using case control methods and paying particular attention to the effects of duration of use and type of HRT undertaken, the authors were still unable to disentangle and quantify these effects precisely.

Buring's study (Buring et al., 1987) found no statistically significant elevated risk of breast cancer either for those undergoing a natural menopause nor for those with one ovary or no ovaries.

2. Duration of use and dose

Studies of the use of diethylstilibestrol and oral contraceptives have suggested that long exposure to hormones may be necessary before any association between use and breast cancer can be seen (Hunt and Vessay, 1987; Kay and Hannaford, 1988). The same association would therefore seem plausible in the case of HRT.

Some of the studies do indeed suggest elevated risks for ORT users. Kaufman's study shows that for women with a natural menopause, more than ten year use is associated with an elevated risk (Kaufman et al, 1984) and similarly, Nomura et al (1986) show an elevated risk after six years. In addition, the studies by Hiatt, for bilateral oophorectomised women, shows an increased risk after three years or more use and Wingo's study also indicates elevated risks associated with use of 15 years or more. Similarly, Buring's

recent study showed higher RR in all sub-groups associated with more than five years duration of use (Buring et al., 1987). However, in all these cases, although the direction of the results indicated a positive association between duration of use and risk, the results were not statistically significant and it is inappropriate to draw firm conclusions from such studies, especially as there are others (see table) which report no such an association.

Of more importance are the results where the elevated risk associated with duration of use has been shown to be significantly different from the risk faced by non-users. This is the case in the study undertaken by Brinton, who looked at 1,960 cases of breast cancer amongst white post-menopausal women who had been recruited into a breast cancer screening programme in the USA. For women undergoing a natural menopause, there was a statistically significant trend of elevated risk with years of use, culminating in 1.70 RR with 15 or more years of use. For all sub-groups (adjusted for age and type of menopause), the risk was again statistically significant, giving a RR of 1.47 with 20 plus years of use (based on 49 cases of breast cancer).

A recent Swedish study (Bergkvist et al., 1989) has received much attention by reporting that women using any form of oestrogens for nine years or more experienced a RR of 1.7.[3] This study is important, as it followed up, for an average of six years, a large cohort of over 23,000 Swedish women who were identified as non-contraceptive oestrogen users. Out of this group, a random sample of one in 30 was chosen for further study, comprising the completion of a questionnaire which was answered satisfactorily by 89% of the sub-group (giving a total of 653 completions). Further analysis was

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(3) The additional conclusions regarding specific types of HRT are discussed in a later section.

undertaken on a matched case-control basis in order to investigate dose-response relationships.

However, this study has been widely criticised, in particular it has been noted that over half the women in the sub-group had taken oestrogen for many years before their base-line prescription status was defined (Barrett-Conner, 1989; Lancet Editorial, 1989). The implication is that the total duration of oestrogen use may well be underestimated in this study. This criticism may also apply to other studies where the type and duration of hormone use prior to the study period chosen is not clarified. In addition, the Swedish research has been criticised on the basis of potential biases in the treatment groups studied. For example, it has been pointed out that the authors did not adjust the analysis for previous use of oral contraceptive oestrogens, which would clearly have a confounding role (Stevenson and Whitehead, 1990). Again, this could also apply to other research in this area. Additionally, a discrepancy was found between the number of women who were prescribed oestrogens (calculated from review of pharmacy records) and thus included in the "user" group, and the number who actually reported using oestrogens. This might cause considerable bias in the relative risks reported for users (Jacobs et al., 1990; Epstein, 1990). Lastly, the failure to give adequate details regarding dose and total duration and severity or stage of tumours in users has also been widely criticised (Simon, 1990; Mauvais - Jarvis et al., 1990).

Two of the older studies also found statistically significant relationships between duration of ORT use and risk of breast cancer, although in Ross' study (Ross et al., 1980), the elevated risk of 2.5 for those with

intact ovaries was related to a dose of 1,500 Total Milligram accumulated Dose (TMD) rather than actual months of use. TMD was measured as the sum of dose, frequency of dose, and duration of use and 1,500 TMD represents the equivalent of three years daily use of 1.25 mg of conjugated oestrogens.

In Hoover's study (Hoover et al., 1981) an elevated RR of 1.7 after five or more years of use was found for women overall and similarly, a risk of 1.8 for those taking doses in excess of 1.25 mg.

It is important to note that although many of the studies do show a trend of increased risk with duration of use or dose, only those yielding results which are statistically significant are reliable.

3. Type of HRT

The majority of research has focused on the use of conjugated oestrogens (ORT), but the Table 1 indicates that some studies also distinguished between various types of oestrogen and more importantly, also considered the use of opposed HRT where progestogens are also administered. Key and Pike (1988) have argued that it is possible that the addition of progestogen may either induce cell mitoses (and therefore increase the risk of breast cancer) or that it will have no effect and thus only oestrogen affects risk of breast cancer. They discuss the evidence for both these hypotheses (especially in relation to combined oral contraceptives) and whilst they do not reach a firm conclusion, they remark that the use of HRT may be "either the same as or more than that caused by ERT" (oestrogen alone) (Key and Pike, 1988). The implication therefore, is that the addition of progestogen does not offer any protective effect in the case of breast cancer (although elsewhere it is shown

that this may not be the case for other types of cancer) and indeed may even increase the risks faced by women taking hormones.

This appears to be supported by the results reported by Bergkvist et al. (1989) who found that out of all 253 women using some form of HRT, who had developed breast cancer, the risk was highest amongst those taking oestrogen and progestogen in combination for a period of time greater than six years. Indeed, as the table shows, the relative risk in this group was 4.4 compared with non-users. In addition, women who had previously used only oestrogens and then switched to the combination regime for three or more years, also had an elevated risk of 2.3. The authors therefore suggest that their results indicate "... a lack of evidence that the concomitant use of progestin reduces the excess risk of breast cancer associated with long-term oestrogen use. However, further research must also investigate the possibility that the addition of progestins to estrogen therapy may increase the risk of breast cancer" (Bergkvist et al., 1989, p. 297).

Although the results appear very suggestive, it is important to note that even the elevated relative risk of 4.4 is <u>not</u> statistically significant due to the small numbers of cases within this group (10 patients). Despite this, it has however been noted (Barrett-Connor, 1989) that these results are also compatible with a Danish study which found an increased relative risk of 1.36 for combined HRT but no increase with ORT use (Erwertz, 1988).

In contrast to these negative findings regarding combination HRT therapy, the work undertaken by Gambrell et al. (1983) outlined earlier, offers an opposing view of the role of progestogen in breast cancer. As illustrated in the table, Gambrell found evidence of a protective effect of

oestrogen, but in particular, a strong protective effect for users of combination therapy (RR of 0.3, compared with 1.4 for non-users and 0.7 for oestrogens alone). The authors point out that other studies may have failed to detect the protective effect of adding progestogen to oestrogen therapy due to inadequate follow-up periods, whereas their study was able to focus on long-term progestogen use. They also report additional evidence from other studies, including details of research with infertility patients with progestogen deficiencies in order to support their theory.

However, as outlined earlier, there are certain methodological flaws which might have biased these results and despite the apparent strong protective effect, the results should be treated with caution. For combined therapy therefore, the overall conclusions must again be mixed - research has shown conflicting results, that the addition of progestogen has a protective effect, no effect or even a harmful effect on breast cancer risk. Nothing more certain can be said until further research concentrates specifically on this aspect of HRT.

Another important factor in considering the risks of breast cancer associated with hormone use, is the suggestion that the stage and grade of breast carcinomas found in users of oral contraceptives is often more favourable than those found in non-users and thus more amenable to therapy (Stoll, 1967). Thus, despite a higher <u>incidence</u> of breast cancer in users, this may not be translated to a higher <u>mortality</u> rate for this group. Indeed, Bergkvist et al., in response to some of the criticism of their breast cancer study, report that the prognosis of women taking hormones who develop breast cancer, is in fact slightly more favourable than in the general population (Bergkvist et al., 1990).

(6) Endometrial Cancer

The increased risk of endometrial cancer associated with the use of ORT is much more well documented and therefore less controversial than is the case for breast cancer. However, whilst it is generally accepted that the available research indicates the existence of an elevated risk of endometrial cancer, what is more debatable is the magnitude of this risk and the type, duration and dose of oestrogen that causes such a risk to arise. In particular, the design of some of the studies in this area has been criticised as causing possible biases in the results and the role of additional progestogen as a safeguard against endometrial cancer is still being debated. These issues are discussed later.

Again, most research has taken the form of case-control (retrospective) studies, matching a group of women with endometrial cancer with a group without such illness for age and other important factors and then calculating relative risks in relation to use or non-use of ORT.

The early, pre-1980s research has been summarised by Jelovsek et al (1980) and also by Hunt and Vessay (1987). It is evident that the majority of these early studies found evidence of an elevated risk of endometrial cancer for those women who had used (mainly conjugated) oestrogens at all and similarly, increased risk associated with longer duration of use or larger doses. Table 2 shows that the relative risk associated with ever-use varied between 1.7 and 12.0. In contrast to the results of breast cancer research, the majority of these results were found to be statistically significantly different from 1.0 at 5% level and so are all equally valid in this sense.

Table 2 : Pre-1980 Research - the relationship between oestrogen use and endometrial cancer

Author(s)	Date	Number of Cases	Relative Risk[1] (where 'no-use' = 1.0)	Association between Risk and:	
				Increased duration	Increased dose
Smith et al	1975	317	7.5*	?	?
Ziel and Finkle	1975	94	7.6*	✓	?
Mack et al	1976	63	8.0*	✓	✓
McDonald et al	1977	145	2.0*	✓	✓
Gray et al	1977	205	3.1*	✓	✓
Wigle et al	1978	202	2.2*	✓	?
Horwitz and Feinstein	1978	268	(a) 12.0* (2) (b) 1.7	?	?
Antunes	1979	451	(a) 6.0* (2) (b) 2.1*	✓	✓
Jick et al	1979	67	11.2*	?	?
Weiss et al	1979	322	5.3* (3)	✓	✓

(1) where possible, relates to conjugated oestrogens (2) See text for explanation of control group
(3) for 1-2 years of use * Statistically significantly different from unity at 5% level

Source: adapted from Hunt and Vessay, 1987

In addition, it is evident that where the issues of risk associated with increasing duration of use or dose were addressed, a positive relationship was found to exist.

Before assessing the probable reasons for such wide variation in results, Table 3 presents the results of post-1980 research on this topic. Once more it is evident that the majority of more recent results show statistically significant elevated risks of endometrial cancer for those who had taken oestrogens. The relative risks are less widely distributed, varying between 1.5 and 4.8[4]. Again, a positive association between increased duration of use and risk was particularly evident, and, to a slightly lesser extent, such a relationship was also found in relation to dose.

A British cohort study of over 4,000 women receiving HRT has compared the 'observed' incidence of endometrial cancer in this cohort, with the 'expected' rate calculated from national data and rates (Hunt et al, 1987). On this basis, the incidence of endometrial cancer in the cohort was almost three times the expected rate (2.84).

The methodological basis of some of the research has, however, been the topic of considerable debate and controversy. In particular, the choice of a control group is of vital importance when interpreting the results presented by the authors of the various studies. It has been noted that the use of oestrogens may in fact provoke uterine bleeding in women with previously asymptomatic endometrial cancer (Horwitz and Feinstein, 1978). As a result

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(4) Excluding the results of Salmi, 1980, which showed a reduced risk but was insignificant at the 5% level.

Table 3 : Post-1980 Research - the relationship between oestrogen use and endometrial cancer

Author(s)	Date	Number of cases	Relative Risk[1] (where 'no-use' = 1.0)	Association between risk and:	
				Increased duration	Increased dose
Salmi	1980	318	0.8	?	?
Jelovsek et al	1980	431	2.4*	✓	X
Hulka et al	1980	256	3.6*	✓	X
Shapiro et al	1980	149	3.9*	✓	?
Stavraky et al	1981	206	(a) 1.5 (2) (b) 4.8*	✓	✓
Spengler et al	1981	88	2.9*	✓	✓
Obrink et al	1981	622	3.7*	✓	?
La Vecchia et al	1982	179	2.3*	?	?
Shapiro et al	1985	425	3.5*	✓	?
Buring et al	1986	188	2.4*	✓	✓

(2) See Table 2

* Statistically significantly different from Unity at 5% level

Source: adapted from Hunt and Vessay, 1987.

of this, such women would then be referred for diagnostic tests which would subsequently confirm the presence of endometrial cancer and result in an increased detection rate for this group. This might therefore bias the results of such studies by showing a far greater incidence of cancer in the oestrogen group, whilst it may in fact be the case that such cancers are also present in the control group but remain undetected due to a lesser degree of diagnostic surveillance in that group.

Horwitz and Feinstein investigated this further by undertaking two separate case-control studies at the same institution, but using two different control groups. The first study chose the subjects in a "conventional" way, i.e. women were selected from a registry of gynaecological cancer and those with endometrial cancer in particular were chosen as the cases. An equal number (119) of women were drawn from the remaining subjects, matched with the cases for age and race. The control group therefore had various other types of gynaecological cancer. The second study used subjects chosen from 6869 women who had undergone either a hysterectomy or dilatation and curettage (D+C) during a two year period. Those with endometrial cancer became the case group and matched controls were then selected from the remaining group of women.

The reason for choosing the particular groups of subjects for the second study is that those women who had undergone a D+C or hysterectomy were therefore all likely to have had any asymptomatic endometrial cancer detected and their inclusion would therefore be unlikely to cause the detection bias outlined earlier.

The results of the 'conventional' and 'alternative' method are presented below in Table 4. The authors point out however that although the risk ratio found in the alternative group (2.30) is indeed very much smaller than the risk calculated by the conventional sampling method (11.98), some "oestrogen-influenced" bias may still exist due to the fact that the presence of uterine bleeding is likely to be a strong stimulus to hospitalisation. In order to adjust for this, the results were further stratified according to the reason for hospitalisation i.e. presence or absence of uterine bleeding. These results are presented in Table 5.

Table 4: Relationship between endometrial cancer and oestrogen use in two alternative samples

Group	Conventional		Alternative	
	Cases	Controls	Cases	Controls
Users (6+ months)	35	4	44	23
Non users	84	115	105	126
TOTAL	119	119	149	149
Risk Ratio	11.98*		2.30*	

* Statistically significant at 5% level.

Source: Horwitz and Feinstein, 1978: Tables 2, 3, 4, 5.

Table 5: Results further stratified for bleeding

Group	Conventional				Alternative			
	UB		NB		UB		NB	
	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
Users	34	1	1	3	43	18	1	5
Non Users	79	25	5	90	99	71	6	55
TOTAL	113	26	6	93	142	89	7	60
Risk Ratio	10.76*		6.00		1.71		1.83	

(1) Uterine bleeding

(2) Non bleeding

* Statistically significant at 5% level.

Source: Horwitz and Feinstein, 1978: Tables 2, 3, 4, 5.

It is evident therefore that one of the reasons for such high reported risk ratios may in fact partly be due to the existence of detection and referral bias which produces exaggerated associations between ORT and the risk of developing endometrial cancer. The selection of 'conventional' control group was indeed the norm for the majority of the other studies presented in the table, but there are some exceptions[5].

(5) Note that Horwitz and Feinstein relate some results from two early (pre 1970) studies that found low relative risks also.

In particular, Antunes et al. (1979) also used two different control groups in their research. Cases were drawn from patients with endometrial cancer and matched with controls from the same hospitals from services other than gynaecology, obstetrics and psychiatry. A second control group was drawn from gynaecology services (excluding endometrial cancer). The relative risks of 6.0 and 2.1 were found for each group respectively and even the lower estimate was statistically significantly different from unity.

Secondly, Stavraky et al. (1981) also used two separate control groups for this reason. One group consisted of women with gynaecological disorders (other than endometrial cancer) and the other of women with non gynaecological disorders. The relative risk associated with oestrogen use of 6 months or more was 4.8 for the general group and 1.5 for the gynaecology group. A similar pattern to the other studies designed in this way is therefore apparent.

A further complication in the analysis of the results and potential biases exists. In response to the hypothesis of 'overestimation' advanced by Horwitz and Feinstein, it has been suggested that a possible source of underestimation of the relative risks of endometrial cancer may also exist (Hutchinson and Rothman, 1978). If the control group selected for the 'alternative' method (i.e. the gynaecologic group) includes women who are suffering with possibly oestrogen-related complaints such as endometrial hyperplasia or proliferative endometrium (which caused the subsequent need for curettage), then it is possible that this group would be more likely to be users of oestrogen than the rest of the population and thus that any estimate of the risk of endometrial cancer among users obtained with this control group would underestimate true risks.

Although Horwitz and Feinstein present a further analysis which excluded this sub-group and indeed find that the risk ratio then rises to 2.00 for the alternative method, they conclude that as this is still far lower than the results from the conventional method, it does not disprove their hypothesis regarding the overestimation of the association between oestrogen use and endometrial cancer. Whilst this is indeed a fair point, it is important to note that whereas the original RR of 1.7 for the alternative group was not found to be statistically significantly different from 1.0 at the 5% level (see Table 2), the RR of 2.00 calculated after adjustment for the existence of hyperplastic and proliferative endometrium is significant at this level.

The previously mentioned study by Stavraky et al. (1981) specifically aimed to address the issue of such potential biases in both directions, by proposing that the 'true' RR would be somewhere between the two estimates calculated with conventional and alternative methods and indeed, this is probably the most valid way of approaching these results. Some further evidence for this approach can be gained by investigating the relationship between past use and risk of endometrial cancer.

Shapiro et al. (1985) point out that the surveillance and detection bias depends upon the investigation of uterine bleeding caused by oestrogen-use. However, as such use cannot provoke bleeding years after discontinuation, then this bias can occur only among current or recent users and any elevated risks found among past users could not be explained solely by such biases. Shapiro's study did indeed find that risks remained significantly high after discontinuation. These findings have been substantiated in some studies, (for example, Buring et al., 1986) but not in others. Thus, as the evidence is

again not decisive, it seems even more important to regard the 'true' risks as lying somewhere mid-way between estimates that have, and have not, been adjusted for potential biases. Indeed, the British Gynaecological Cancer Group concluded that such a bias could account for only "a small part of the observed association" (BGCG, 1981).

Turning now to the effect of duration of use and dose upon the association between oestrogens and endometrial cancer, the overall picture to emerge is the existence of a strong positive association. Although such relationships were often not examined in the earlier studies, when they were, the results were usually positive. For example, Gray et al. (1977) found that RR rose from 1.2 for between 0-4 years of use to 11.6[6] for 10+ years. Similarly, McDonald et al (1977) found a RR of 4.9 for duration of 6 months to 1 year and 7.9 for 3 or more years use. Similar results were also presented by Weiss et al. (1979), reporting an elevated risk of 8.3 for 20+ years of use and only 1.2 for 1-2 years use and Antunes et al. (1979) finding a 15 fold increase in risk for users of 5+ years. More recently, Buring et al. (1986), reported an elevated RR of 1.4 for use of less than 1 year compared with a RR of 7.6 for 10+ years of use.

The British cohort study (Hunt et al., 1987) also found an association between duration of use and incidence. Women who had been receiving ORT for 0-4 years had an incidence of 2.11 times the expected rate but this rose to 5.71 for 10+ years of use. The authors note however that the trend did not quite reach statistical significance in this case.

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(6) Statistically significant at 5% level.

Very similar results have been found in relation to dose, with the majority of studies focussing upon higher risks faced by women taking oestrogens in daily doses in excess of 0.625 mg. Indeed, Buring et al. (1986) find the highest RR of all (8.7) for women using higher dose preparation for longer durations.

So far, the discussion has focused upon ORT (mainly conjugated oestrogens), as the majority of the studies collected data in mid to late 1970s, when this was the most common regimen (at least in the USA, where most of the research has originated). The number of women taking progestogen as an addition has generally been too small to allow any valid analysis to be undertaken. However progestogen has been shown clinically to prevent hyperplasia and cause regression of pre-existing adenomatens hyperplasia for many patients (Henderson et al., 1988b). In addition, in pre-menopausal women taking oestrogen alone as a contraceptive, risk of endometrial cancer has been shown to rise; but in women taking combined oral contraceptives (oestrogen and progestogen), the risk is decreased (Henderson et al., 1983).

Apart from scientific and clinical studies, few epidemiological studies of oestrogen and progestogen (HRT) have been undertaken. However, the studies that have been published, do indeed suggest a protective effect of progestogen in the case of endometrial cancer (e.g. Sturdee et al., 1978). The results of a prospective British study of 745 women taking various forms of hormone treatment for the menopause also supports this (Paterson et al., 1980). Endometrial biopsies were performed on all women and the incidence of hyperplasia (this is commonly accepted as a possible precursor of endometrial carcinoma) was noted. The authors found that the addition of progestogen

significantly reduced the incidence of hyperplasia in women receiving oestrogen either orally or as an implant. Moreover, the incidence of hyperplasia for the HRT group was only 1.2% compared with the high dose ORT group where incidence was 14.8%.

Of great interest and importance is another UK study reported by Hunt et al. (1987). In a cohort study of 4544 women receiving some type of HRT, 14 were diagnosed as having endometrial cancer (three times the expected rate). Of these, eight had taken therapy which was mainly or entirely opposed (i.e. addition of progestogen to oestrogen). A detailed analysis of the treatment histories revealed that only one of these women had received an opposed regimen which would now be considered as sufficiently protective to the endometrium (either due to the prescription of progestogens for too few days in each month or due to ineffective preparations). Thus, as the authors note, it is even more essential that research continues to focus on exactly what is an adequate regimen in this case, as women receiving inadequate progestogen prescription may not only be deprived of the potential protective effects on the endometrium, but may also be exposed to possible reductions in the protective effect of oestrogen-only regimens on the cardiovascular system.

A recent consensus report concerning progestogen use produced by 56 participants of international repute, stated that progestogens were indicated for opposing the effects of oestrogen on the endometrium (Whitehead and Lobo, 1988). However, due to its unknown effects on the cardiovascular system (this is examined later in this paper in detail) and the uncertain protective effects on breast cancer and osteoporosis, the routine addition of progestogen was advocated only for those women with an intact uterus.

A final point to be made relates to the stage of endometrial cancer found in users of HRT as opposed to non-users and the resulting mortality rates for the disease. Some research indicates that the cancers found in ever-users of oestrogen therapy are early-stage cancers and thus have a more favourable prognosis. For example, La Vecchia et al. (1982) found that the RR was higher for stage I cancer (2.7) than for stages II-IV (1.6) and similarly higher for histological grade 1 rather than 2 or 3. Moreover, the incidence of invasive cancer and lymph node involvement was also lower in the user group.

Buring et al. (1986) also examined this hypothesis and found that the highest risk was again confined to stage I, grade 1 disease, with no myometrial invasion. However, it must be noted that the longer term users in this study did begin to exhibit increases in the risk of more advanced disease. Several reasons for the apparent association of oestrogen use and low grade, early endometrial cancer can be considered. Firstly, it may be possible that due to the extra medical surveillance of ORT users, cancers are detected at an earlier stage than would otherwise be the case. This is related to the argument outlined earlier. Secondly, it is often hypothesised that some types of endometrial hyperplasia could be misclassified as early endometrial cancer and thus inflate the RR for low stage and grade tumours. The degree to which this might be true obviously depends upon the methods of classification and investigation used in the studies. Finally, it is also possible that the type of cancer arising with the use of oestrogens <u>is</u> in fact less aggressive than other types.

(7) Heart Disease

There are several biological reasons why non-contraceptive oestrogens are likely to influence the risk of cardiovascular disease and the evidence for each has been assessed (Bush and Barrett-Connor, 1985). Firstly, and probably most importantly, 30 years of research has shown that oestrogens can lower total cholesterol and low density lipoprotein (LDL) cholesterol and raise high density lipoprotein (HDL) cholesterol. As high levels of HDL are protective and high levels of LDL increase cardiovascular disease risk, this suggests a very positive protective effect of exogenous oestrogens. Secondly, it is possible that oestrogens can have an adverse effect on cardiovascular disease risk by changing carbohydrate metabolism, but this is less certain (Bush and Barrett-Conner, 1985). Lastly, oestrogens may adversely affect both blood coagulation and blood pressure, but once more the evidence is contradictory, especially for blood pressure, as studies have shown both increases and decreases in the blood pressure of post-menopausal oestrogen users.

In addition to the above data concerning the effects of exogenous oestrogens, it is also possible that endogenous oestrogens affect the risk of cardiovascular disease, and again, Bush and Barrett-Connor have reviewed the evidence for this. In particular, the sex differential in the risk of death from cardiovascular disease, (favourable to women) suggests a protective role for oestrogens. Additionally, numerous studies have addressed the question of whether women who have lost ovarian function (via surgical or natural menopause) and thus cannot produce significant amounts of oestrogen, are at higher risk of cardiovascular disease. Whilst the majority have found this to be the case, several methodological problems make definite conclusions

difficult.[7]

Given the theoretical and biological indications above, much research relating ORT and HRT to changes in the risk of cardiovascular disease in menopausal women has been undertaken and Table 6 presents the results. It is apparent that the majority of statistically significant results indicate a protective effect for ORT, whether the endpoint is fatal or non fatal disease. However, once more interpretation of the results is again complicated by various methodological difficulties in the design of some of the research. It has been argued that such differences might account for the fact that two of the largest research studies (Nurses Health Study and the Framingham Study) found directly opposing results (Stampfer et al., 1985; Wilson et al., 1985).

The major controversy surrounds the issue of patient selection in the medical prescription of HRT. Women who fall into a high risk group for heart disease (such as those with hypertension, diabetes, angina) are unlikely to be receiving HRT as such contra-indications would mean doctors would be wary of prescribing HRT at all. On the other hand, those who do receive HRT are therefore likely to be at lower risk of CHD anyway and it has been argued that if results are not adjusted for these factors, then any detrimental effect of HRT will be underestimated. The results would then be biased in favour of HRT and its apparent protective effect would be the result of patient selection rather than a true causal relationship. However, adjustment for known risks of CHD are usually made in the studies that are reported in Table 6 and the protective effect of ORT seems to exist even after such allowances are made (e.g. Henderson et al., 1988a; Paganini-Hill et al., 1988).

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(7) For further details see Bush and Barrett-Conner, 1985.

Table 6 : The Relationship Between HRT[1] and Cardiovascular Disease

Author(s)	Date	Study design	Number of Cases	End points	Relative Risk (where 'no use' = 1.0)
Burch et al	1974	Cohort	9	Fatal CHD	0.43*
Rosenberg et al	1976	Case control	336	Nonfatal MI	1.0 (current use)
Pfeffer and van der Noort	1976	Case control	210	Nonfatal stroke	1.1
Pfeffer et al	1978	Case control	185	MI	0.86
Jick et al	1978	Case control	17	Nonfatal MI	7.5* (current use)
Gordon et al	1978	Cohort	36	CHD	1.6
Hammond et al	1979	Cohort	58	CAD	0.33*
Petitti et al	1979	Cohort	26	MI	1.2 (current use)
Rosenberg et al	1980	Case control	477	Nonfatal MI	1.0 (current use)
Ross et al	1981	Case control	133	Fatal IHD	0.43*
Adam et al	1981	Case control	76 23	Fatal MI Fatal SH	0.65 0.63
Bain et al	1981	Case control	123	Nonfatal MI	0.7 (current use) 0.9 (ever)
Szklo et al	1984	Case control	39	Nonfatal MI	0.6
Stampfer et al	1985	Cohort	90	Fatal CHD Nonfatal MI Total CHD	0.6 (ever) 0.3 (current) 0.5* (ever) 0.3* (current) 0.5* (ever) 0.3* (current)

Table 6 (continued)

Author(s)	Date	Study design	Number of Cases	End points	Relative risk (where 'no use' = 1.0)
Wilson et al	1985	Cohort	116 51 194 48 45	CHD MI Total CVD Fatal CVD Stroke	1.90* 1.87 1.76* 1.94 2.27*
Henderson et al	1986	Cohort	84	Fatal MI	0.50*
Petitti et al	1986	Cohort	37	Fatal CVD	0.50
Bush et al	1987	Cohort	50	Fatal CVD	0.37*
Hunt et al	1987	Cohort	20 14	Fatal IHD Fatal stroke and cerebrovascular	0.48* 0.65
Paganini-Hill et al	1988	Cohort	63	Fatal stroke	0.53*

IHD: ischaemic heart disease
CHD: coronary heart disease
CVD: cardiovascular disease
MI: myocardial infarction
CAD: coronary artery disease

* Statistically significantly different from 1.0 at 5% level.
(1) Mainly unopposed conjugated oestrogens.

Despite this, it has been argued that patient selection might still be a source of confusion if unknown risk factors are influencing the results. Petitti has argued that their results indicate a protective effect of postmenopausal oestrogen use on mortality from accidents, homicide and suicide and that this can only be explained by assuming that the oestrogen users were more healthy than the non-users in ways that have not been quantified and thus cannot be adjusted for (Petitti et al., 1986). Their conclusion therefore, is that disparate results might be due to such unknown selection of populations and that ultimately a randomised clinical trial would be the only source of a definitive answer regarding the effect of HRT on CHD.

Further explanations of contradictory results again relate to failure to adjust for factors associated with risk of CHD, this time the effects of type of menopause and age at menopause (Pike et al., 1986; Thompson, 1986). Pike et al. note that previous evidence has indicated that at any given age, women who have a natural or surgical menopause have a much higher risk of CHD compared with pre-menopausal women. In addition, it has been reported that early menopause is also positively associated with the risk of CHD and thus as postmenopausal oestrogen use is associated with early menopause, it will seem to be also associated with an increased risk of CHD. Pike points out that in order for a protective effect of oestrogen use to be observed, it would have to be strong enough to overcome the underlying positive association unless adjustments in the data are made for type and age at menopause.

Others have suggested additional reasons for discrepancies between the two large studies mentioned earlier. The Framingham study collected data between 1962 and 1972 which was a period of optimism about the beneficial

effects of oestrogen use on CHD, whereas the Nurses Health Study studied data collected in a later period when such optimism was tempered (Van Hemert, 1986). The discrepancies could therefore be due to the preferential prescribing of HRT during the "Framingham period" to women who were particularly aware of the risk of heart disease, such as those who had previously lost a relative due to heart disease.

An interesting addition to the debate is the research undertaken, again using the Nurses' Health Study data, by Colditz et al. (1987) which looked primarily at the risk of heart disease for postmenopausal, as compared with premenopausal women. However, the use of ORT and its role in mediating the risk of CHD was also considered. The authors considered both non-fatal myocardial infarction and fatal coronary heart disease and found that after adjusting for age and cigarette smoking, women with a natural menopause had no appreciable elevated risk of CHD compared with the risk for premenopausal women (RR = 1.0). However, women who had undergone bilateral oophorectomy and had never used oestrogen therapy did exhibit a significantly greater risk than premenopausal women (RR = 2.2),[8] but in oestrogen users, this risk was reduced. Table 7 shows risk ratios for CHD after adjustment for age, smoking and other risk factors for CHD.

It is apparent that after multivariate adjustment, none of the RR reach statistical significance at the 5% level. However, the reduced risk associated with ever-users in the bilateral oophorectomy group, does suggest that the protective effect of oestrogen may exist, and may reduce the excess risk otherwise associated with bilateral oophorectomy due to the rapid

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(8) After adjustment for age and smoking - significant at 5% level.

reduction in endogenous oestrogen production.

Table 7: Risk of CHD (where comparison group is premenopausal women with RR = 1.0)

	Use of Postmenopausal oestrogen	
	Never	Ever
Natural menopause	1.1	0.8
Hysterectomy and bilateral oophorectomy	1.7	0.7
Hysterectomy with or without oophorectomy	0.7	1.8

Source: Colditz et al., 1987.

One important issue which is still controversial is the effect on cardiovascular disease of the addition of progestogen to oestrogen. As previously mentioned, the addition of progestogen is thought to be advisable for women with intact uterus in order to offset the potential deletrious side effects of endometrial cancer and hyperplasia (Whitehead and Lobo, 1988). However, the elevated risk of vascular disease seen in users of oral contraceptives is related to the progestogen component of the pill (Henderson et al., 1986). It is thought that progestogen can have the opposite effect of oestrogens on high and low density lipoproteins, therefore possibly negating the protective effective of unopposed oestrogen therapy.

Indeed, it has been suggested that, in order to calculate the appropriate net beneficial effect of opposed HRT, it is reasonable to assume

that the beneficial effects conferred by oestrogen during the 28 day cycle are negated during the 10 days in which progestogen is added (Henderson et al., 1988b).

Such possibilities are of particular importance in the light of the findings of the large U.K. study of over 4,500 HRT users (Hunt et al., 1987). Forty-three per cent of the HRT taken by women in this cohort was opposed, but in some cases, the dose and administration of progestogen was considered to be inadequate. Thus, not only would the beneficial effects of the progestogen on endometrial cancer be limited, but the detrimental effects of the progestogen on the risk of cardiovascular diseases may also be substantial, although this was not in fact, reflected in the mortality rates from ischaemic heart disease in this particular study.

A further complication arises from consideration of the route of administration of oestrogens, as it has it been suggested that the favourable effects of oral oestrogens on HDL and LDL may not be found to such a large extent if oestrogens are delivered transdermally or percutaneously (Ross et al., 1989; Stampfer and Sacks, 1988). However, oestradiol implants do seem to have the same protective effects as oral oestrogens (Whitehead and Fraser, 1987).

It is apparent that the weight of evidence seems to suggest a favourable effect of ORT on cardiovascular disease (Whitehead, 1988; Bush, 1986), which is complicated by the possibility of the negative effects of progestogen in opposed HRT and the potential weaker effects of oestrogen delivered by particular routes.

(8) HRT use and Mortality

In previous sections of this paper, the relative risks associated with ORT and HRT use have been explored in relation to heart disease, osteoporosis, breast cancer and endometrial cancer. ORT and HRT use appears to be associated with elevated risks for some conditions and reduced or no risks for other conditions, and it is commonly thought that the decision to prescribe or not should therefore always involve the weighing-up of the relative risks and benefits for the individual patient.

It is apparent that whilst there does indeed seem to be increased risks of developing cancer (especially endometrial cancer) associated with some forms of oestrogen use for some patients, the tumours are often of an early stage and are less invasive and thus much more amenable to treatment. As outlined earlier, it is unclear whether HRT users actually develop tumours which are less invasive per se, or whether early detection via regular contact with medical services in the course of HRT use, means that tumours are detected at an earlier stage.

Whatever the cause, it seems that on balance this may be one reason for the favourable mortality profile of HRT users. The UK study of a cohort of HRT users showed that overall mortality rates for all causes were low in this cohort, indeed when compared to expected mortality (calculated for the cohort from age-specific population rates), the relative risk was 0.59.[9] (Hunt et al., 1987). The authors have several reservations about the findings, in particular remarking, as others have done, than the users of HRT might be a

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(9) Statistically significant at 5% level.

"self-selected" group who differ in a non-random way to those women in a non-user group. The group of users may be much more healthy than non-users as women at 'high risk' (who have contraindications to HRT) would not be prescribed such therapy. However, if this was indeed the case, they point out that the effect should decline with time, but fail to find evidence of this in their study (although they do point out the relatively short duration of follow-up which may mean such effects will become apparent later).

An additional selection bias might have occurred in this particular cohort of women as they were all long term users of HRT who were attending specialist menopause clinics in the UK. Hunt et al remark that this is likely to be an atypical group given the inequality of access to clinics and other sources of HRT both regionally, and also by social criteria. Indeed, the cohort exhibited a high social class distribution, but the authors did attempt to adjust for such biases and the relative risks reported in the analysis all take account of these factors.

Several other factors also cause concern, especially the particularly low risk of death from breast cancer despite the high incidence of the disease in the cohort (see section on breast cancer). Whilst it may well be the case that detection was earlier for this group (and this was supported by the finding that the stage of tumour was relatively favourable) the authors do not believe that this is sufficient to explain more than a small part of the excess incidence found and they believe that in the future, the mortality from breast cancer will rise in this cohort.

Others have also investigated overall mortality rates amongst HRT users in the USA. Bush et al. (1983) investigated the relationship between mortality, hysterectomy status and oestrogen use in over 2,000 women who had been followed up for an average of $5^1/_2$ years. The results are summarised below:

Table 7: Age-adjusted mortality rates (per 1000 per year) according to oestrogen use

	No use	Use	Total
No hysterectomy	9.0	4.9	8.2
Hysterectomy	8.2	2.8	5.7
Oophorectomy	11.8	1.4	7.2
Total	9.3	3.4	-

Source: Bush et al., 1983.

In all cases, it can be seen that oestrogen users had a lower mortality rate than non-users and irrespective of hysterectomy status, the mortality rate in users was 0.37 times that in non-users (statistically significantly different from unity at 5% level). This difference remained even after adjustment for other risk factors such as smoking.

Once more, the authors attempt to adjust their analysis to control for possible selection biases. However, they found that the relative risk remained low even when the analysis was confined to deaths occurring later in the following period (thus a "healthy base-line" effect does not seem to be the cause of the favourable profile). After examining records for indications of higher cardio-vascular morbidity in non-users (which would also cause a

selection bias) they could find no evidence that non-users were at higher risk of death from this cause at baseline.

A more recent study, also undertaken in the USA again found a lower risk of death from all causes in oestrogen users when compared to non-users (Criqui et al., 1988). The relative risk for users was estimated at 0.69 (statistically significant at 5% level), but after adjustment for the relatively favourable risk profile of users at base-line, the RR became 0.79 (just failing to reach significance at 5% level). The analysis also investigated the effects of smoking, finding a very strong protective effect of oestrogen on cardiovascular disease in current smokers but not past smokers.

The large American research studies outlined earlier (Wilson et al, 1985 and Stampfer et al., 1985) also examined overall mortality rates, in oestrogen users. Stampfer reports that women who had ever used hormones and who currently used them had lower relative risks of total mortality than non-users. However, the authors note that this was primarily due to the large number of deaths amongst those women who had cancer at base-line and thus were not likely to have been prescribed oestrogens. Once these (and women with coronary disease at base-line) were eliminated from the analysis, the age-adjusted RR for ever use was 0.9 and for current users, 0.7 (latter significant at 5% level; former not significant).

Similarly, in the Framingham study (Wilson et al., 1985), all cause mortality rates did not differ significantly between users and non-users, once adjustments for all risk factors were made.

Overall, the results of the American studies seem contradictory, whereas the large UK study does indeed seem to illustrate an overall mortality advantage to long-term HRT users, despite the caveats due to selection bias and the possibility of higher mortality rates becoming apparent once further follow-up data is available.

(9) Overall Cost and Effectiveness

Table 8 shows an illustrative set of calculations for induced changes in the incidence of certain conditions for a cohort of 100,000 females aged 65-74, taking combined HRT for 10 years.

Table 8: Estimated changes in annual incidence induced by combined HRT for 10 years

Condition	Annual incidence/100,000 females aged 65-74	RR[3]	Change in incidence/100,000
Breast cancer	206.1[1]	1.40	+82
Hip fracture	230.4[2]	0.50	-115
Ischaemic heart disease	849.6[2]	0.55	-382
Cerebrovascular disease	660.0[2]	0.50	-330
Net change			**-745**
Variant 1			
Ischaemic heart disease	"	0.70	-255
Net change			**-618**
Variant 2			
Breast cancer	"	1.00	0
Net change			**-827**
1 and 2 Combined			
Net change			**-745**

(1) Cancer statistics - registrations 1984 MBI No. 16, OPCS, 1988.

(2) Hospital in-patient enquiry 1985 MB4 No. 27, OPCS, 1987.

(3) Representative estimates from the literature reported in previous sections of paper.

Notes to Table 8

(1) Ideally, the incidence rates reported should be adjusted to take account of the proportion of women already facing higher or lower risks of these conditions due to prior or current use of HRT. However, without details of the age of profile of HRT use and the preparations used, this has not been possible, but in view of the small overall proportion of uses, it is not likely to have a significant effect on the results.

(2) It should be noted that, especially in the case of osteoporotic hip fractures, 10 years use of HRT will produce its main effect during the latter years of the patients life. In a more complicated, computer-aided modelling process, this may be taken into account (for example, Weinstein and Schiff, 1983; Hillner et al., 1986) but is not possible in the scope of this paper and with available data. However, this implies that the beneficial effects are an underestimate of the true effects.

(3) Oestrogen alone would be the preferred prescription for those women with prior hysterectomy (due to the uncertain effect of progestogen on the risk of breast cancer and on the cardiac system). The more favourable results presented first in the table can thus be taken as applying to this group of women receiving oestrogen alone. However, the costs of oestrogen only prescriptions would be lower. This is considered later.

It resembles a similar analysis undertaken for the USA by Henderson et al. (1988b) but rather than reporting mortality rates it reports incidence rates (in fact the relative risks used by the above authors in adjusting mortality rates are mostly taken from the literature pertaining to incidence rather than mortality). A further difference is that the risks of endometrial cancer from the use of unopposed oestrogen in women with an intact uterus is excluded from the analysis in Table 8. The rationale for this is that this regimen is now extremely unlikely to be prescribed and thus unopposed oestrogen would only be given to women who had undergone a hysterectomy.

By using such an analysis, it can be seen that the use of HRT can produce an annual reduction in the net incidence of these three conditions, of 745 cases. The subsequent rows show alternative assumptions made regarding the RR faced by HRT users. Firstly, as it has been suggested that the addition of progestogen can reduce the beneficial effect of oestrogen on heart

disease, Variant 1 assumes a less protective effect of HRT. Due to the high incidence of this disease, even a relatively small change substantially reduces the overall beneficial effect of HRT on incidence rates. Evidently, more information regarding the cardiovascular effects of combined HRT is essential in refining the illustrative estimates presented here.

The second variant allows the risk of developing breast cancer associated with HRT use to fall to zero. This relates to the studies outlined earlier which found no adverse effects of progestogen on breast cancer risk. If future work were to support a protective effect on breast cancer risk (as suggested by some authors and discussed earlier), then of course this could also be translated to a positive rather than a negative effect on incidence.

It is evident that the induced changes in incidence will affect both morbidity and mortality, but leaving aside this distinction initially, it is possible to provide some general estimates of the financial consequences associated with the induced changes in incidence.

Estimated costs

The prescription of oestrogen and progestogen will cost, on average, £46 per person, per year (Drugs and Therapeutics Bulletin, 1988). In addition, it is assumed that monitoring of HRT users will necessitate two visits per year to a general practitioner, costing £4.56.[10] The total annual costs of £50.56 per person should however be discounted in order to arrive at the present value of this sum as costs occur over a 10 year period. This

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(10) Calculated on the basis of GP average target income and average time per consultation - A. Shiell (unpublished).

takes account of the fact that money spent in the future is associated with a lower opportunity cost than money spent now (for further details see Drummond et al., 1987). If the total costs of HRT for each women are discounted at 5% over 10 years, the present value of the cost of HRT is £390.42.

One way of approaching the costs of treating the conditions affected by HRT use is to examine the average length of hospital stay for discharges and deaths from each condition. The relevant information is summarised below:

Condition	Mean duration of stay[1] in days for females aged 65-74 years
Breast cancer	10.6
Hip fracture	22.8
Ischaemic heart disease	10.5
Cerebrovascular disease	60.2

(1) Calculated for 1985 from HIPE, 1988.

Using the average cost per in-patient day[11] for acute hospitals of an average size, the total induced costs or savings can be estimated as follows:

Condition	Average annual cost per case of hospitalisation	Discounted cost
Breast cancer	£1056	£815
Hip fracture	£2271	£1754
Ischaemic heart disease	£1046	£808
Cebrovascular disease	£5996	£4632

(11) Source: Health Service Costing Returns, 1987. DHSS, 1988. Inflated to 1988 prices.

The extra costs associated with the prescription of HRT for 100,000 women over 10 years can be calculated as £39,042,000.

It has been estimated that each year an additional 82 women will incur breast cancer, which gives a total extra (discounted) cost of £668,300 in 10 years. Thus, the total direct and induced additional costs of HRT for 100,000 women for 10 years is £39,710,300 (or £397.10 per woman for 10 years treatment).

Offset against this is the annual reduction in the incidence of hip fracture and heart disease. Calculating the cost savings from an annual reduction of 115 hip fractures for 10 years, gives a discounted cost of £2,017,100. Adding the cost savings from an annual reduction of 382 cases of heart disease at a discounted total cost of £3,086,560, and from an annual reduction of 330 cases of cerebrovascular disease at a discounted total cost of £15,285,600, gives a total 'saving' of £20,389,260 (or £203.89 per woman for 10 years treatment).

Subtracting the direct and indirect costs of HRT, gives a net cost of £19,321,040 which is equivalent to £193.21 per woman or just over £19 per woman per year for 10 years. These results are summarised below, along with the implications of assuming that combined HRT has a less protective effect on heart disease that ORT alone, but a protective effect on breast cancer.

Table 9: Estimated changes in costs from 10 years HRT use for 100,000 women

	Cost/savings (£) per woman per year for 10 years
HRT treatment	+ 39.04
Breast cancer	+ 0.67
Hip fractures	- 2.02
Heart disease cases	- 3.09
Cerebrovascular disease	- 15.29
Net cost	**£ 19.31 per woman per year for 10 years**

Table 10: Estimated changed in cost from 10 years HRT use for 100,000 women assuming Variant 1 and Variant 2

	Cost/savings (£) per woman per year for 10 years
HRT treatment	+ 39.04
Breast cancer	+ 0.00
Hip fractures	- 2.02
Heart disease cases	- 2.06
Celebrovascular disease	- 15.29
Net cost	**£ 19.67 per woman per year for 10 years**

The net cost of the 10 year package is therefore quite modest at around £190 per woman over the 10 year period.

One interesting variation is to consider the cost of oestrogen only therapy (ORT) which would be prescribed for women who have had a hysterectomy. The cost of ORT is less than HRT (£11 per year plus 2 GP monitoring visits, which gives a total discounted cost of £155.33 for 10 years treatment) and the more favourable assumptions concerning the protective effect on heart disease can be assumed. After taking these factors into account, Table 11 shows that

a net saving from ORT may be produced:

Table 11: Estimated changes in costs from 10 years ORT use for 100,000 women

	Cost/savings (£) per woman per year for 10 years
HRT treatment	+ 15.53
Breast cancer	+ 0.67
Hip fractures	- 2.02
Heart disease cases	- 3.09
Cerebrovascular disease	- 15.29
Net saving	**£ 4.20 per woman per year for 10 years**

This amounts to just over £40 saving per woman for the complete ORT package. In view of the large numbers of women undergoing hysterectomies who would therefore be likely to receive ORT rather than HRT, this may have significant resource implications.

It is evident that these results can only be considered as indications of both the effectiveness and costs of HRT and ORT. In the first instance, the estimates of relative risks must be considered in the light of the evidence presented in the other sections of this report. In particular, the evidence concerning the effects of combined HRT rather than ORT only is extremely patchy and also more applicable to US prescription patterns than UK. It is reasonable to assume that where oestrogens alone are given (i.e. to those with prior hysterectomy), the more favourable effects on heart disease will be conferred.

Secondly, the costs presented represent broad averages (based on average length of stay) and should not be taken as definitive measures of the cost

consequences. Having said this, the framework allows for changes in both RR and cost estimates to be made (such as those made under variants 1 and 2) easily if more details or reliable information became available.

Evidently, a proportion of women who may develop breast cancer as a result of HRT will die from their disease and thus there will be mortality as well as morbidity effects. In the case of breast cancer, it has been indicated that tumours occurring in HRT users often tend to be present at an earlier stage and when they are less invasive than tumours found in the non-user cohorts of women. For heart disease, the results presented in earlier sections of the paper indicate that the risk of fatal heart disease is of similar magnitude to the risk of non-fatal events, and thus beneficial mortality effects may be produced.

However, even where mortality rates may not be as high, for example, in the case of hip fractures, it is difficult to calculate the direct contribution of hip fracture to mortality due to the fact that obviously those affected are old and often have poor health generally which increases the risk of sustaining a hip fracture initially. However, in the USA, it has been estimated that an extra 12-20% of people sustaining hip fractures die within the first year, compared with expected deaths on the basis of age alone (Cummings, 1985). However, even if mortality rates as a direct consequence of fracture are relatively low, the excess morbidity associated with this condition will indeed be very high, as many people will lose their mobility and thus their independence as a result.

This has profound implications for health and social care resources, as in addition to the hospital costs outlined earlier, the costs of community

care and institutional care could be enormous. Indeed, given the high cost of institutional care, any such 'savings' induced through the prevention of fractures is likely to swamp the net costs shown in the table and produce overall net savings from HRT. However, although there are many cases of hip fracture patients in institutional care, it is not possible to calculate the resource costs averted by HRT use as data regarding the proportion of admissions to long term care due to hip fracture is not available.

Indirect costs and benefits may also arise from the changing incidence of morbidity and mortality associated with HRT use. In particular, it could be argued that reductions in premature mortality and improvements in quality of life attributed to HRT use, allow women to remain in the labour force and contribute to productive output for a longer period of time than would be the case if they had died prematurely, or had left the labour force due to their experiences of disruptive menopausal symptoms.

Whilst this may of course be the case, there are two difficulties associated with the measurement and valuation of such indirect benefits. Firstly, it is far from certain that such production losses would actually occur, especially with high levels of unemployment implying that the replacement of workers could be undertaken very easily and at little cost to society. Secondly, even if production losses or gains could be measured, how will they be valued? Whilst it is true to say that the valuation of productive capacity using earnings data has a long history in the health economics field (see, for example, Rice, 1966; Hartunian et al., 1981), this methodology and its associated bias towards the high income and employable sectors of society and away from the old and low income sectors has been severely criticised and is not recommended (Drummond, 1981; Shiell et al., 1987).

Quality of life

It is evident that in addition to the mortality associated with the above conditions, considerable impact will fall on morbidity and quality of life. In addition, the major reasons for prescription of short-term HRT is to reduce or eliminate the distressing symptoms associated with the menopause and thus one of the benefits of HRT use which will not be captured by mortality effects is the improvement in the quality of life experienced by women who find relief from symptoms. Very little UK research has focused on this issue, but it is evidently of great importance and has a major impact on women's lives.

The negative impact on the quality of life of women who develop breast cancer is obviously important, but must be weighed up against the negative effects of heart disease and hip fracture which may be averted by HRT use. The subjective feelings of women concerning the trade-off between improvements in quality of life and the relative risk of developing breast cancer, but possibly avoiding hip fracture or cardiac disease, have not been systematically addressed and remain unknown to date. However, this is probably the area that is most likely to yield important information regarding the real benefits and costs in terms of quality of life to users of HRT.

Summary

It is evident that the use of HRT entails costs and financial benefits which are distributed throughout the health and social care system. The immediate costs of prescribing HRT for women falls upon the GP and with the introduction of GP drug budgets, this obviously has important implications.

The financial benefits which may arise from reduced hospitalisation and institutional care for hip fractures or heart disease will not accrue to the GP and thus there is no direct financial incentive to prescribe. However, if GPs are aware of the possibility of the offsetting cost effects in the wider NHS system, and if they focus on the improvements to be gained in the quality of life for many women, there should not be a disincentive to prescribe HRT.

(10) Future Information Requirements

Throughout this paper the absence of information relating to certain aspects of HRT has been noted at various points and obviously any future research that filled such gaps would be useful for further analysis. However, the following key areas can be highlighted:

1. There is no substantial and systematic evidence regarding the impact of HRT use on the quality of life of short-term users taking HRT for symptom relief. Although it is generally recognised that this has a major impact on women's lives, there is limited evidence regarding the value placed by women on achieving relief from symptoms. It is important to balance the net costs of HRT against such non-financial benefits.

In addition, use of progestogens can cause periodic bleeding which may reduce the extent to which women feel their overall quality of life has been improved. This has not been addressed and it is not known how often GPs for example, are consulted by women wishing to terminate HRT use for this reason.

It seems reasonable to suggest that this type of research should take place either in the GP setting or in specialist menopause clinics where women's attitudes, expectations and experiences of HRT use could be elicited. Ideally, such work would proceed on a prospective basis, identifying new users of HRT at the pre-treatment level and monitoring their subjective experiences of treatment through time.

2. In relation to this issue, it is important to know how women value the overall relative changes in the risks they may face by taking HRT. Would

women, for example, think that a possibility of 30% increased risk of breast cancer is outweighed by the reduced risks of hip fracture or heart disease? And how are their assessments influenced by the effects on quality of life which are more immediate to them? Or how much of an increased risk of breast cancer might they be willing to accept in order to gain the other benefits?

It is possible to elicit such responses and valuations by presenting alternative hypothetical scenarios to groups of women in order to discover the risk profile which would induce them to accept or refuse HRT. Indeed, such trade-off exercises have begun to show that women tend to be more concerned about accepting something associated with increased risks of a disease than they are about failing to take advantage of something that could decrease their risks of other conditions (R. Lilford, St. James, Leeds; informal seminar, York University). This would suggest that if women were presented with explicit information about HRT they may be more reluctant to accept it than might otherwise have been thought. Of course, the associated impact upon their immediate quality of life would very likely influence such decisions in favour of HRT if women were currently suffering from distressing symptoms.

3. A further issue of vital importance is the lack of information from case control or cohort studies relating to the type of preparations which are now being used in the UK. Much of the existing data is either quite old and represents prescription patterns which would now be considered unacceptable, or is derived from the USA where again prescription patterns are likely to be unrepresentative of UK practice. Even the large UK study of HRT use (Hunt, 1988) recognises that many women had received inadequately opposed therapy which would not be prescribed today.

4. In addition to the content of current prescriptions, new routes of administration, such as the "patch" are becoming more common and once more, little information exists on women's evaluation of their experience with different modes of treatment nor indeed about differential relative risks associated with alternative modes. Whilst such research on the relative risk profiles associated with more recent methods of treatment will obviously not provide any immediate results due to the lag between HRT use and the occurrence of adverse and beneficial side effects, it could be initiated now in order to provide data in the future.

5. The assessment of the relative risks and benefits (and thus also the associated costs) of targeting particular groups of women for HRT would be facilitated by a greater medical understanding of the indications of 'high risk' factors for conditions such as osteoporosis. Although some of these factors have been mentioned in the earlier section of the report, it is evident that the ability to target and select for treatment the high risk women will greatly affect the cost-benefit equation. For example, the introduction of bone scanning equipment may facilitate the identification of this group, but of course will also add to the total cost to the NHS of the HRT package. Experience of the use of such devices is insufficient at present to allow even any tentative conclusions to be drawn, however an important opportunity to monitor the effect of HRT use on the high risk groups identified in this way would be missed if no systematic evaluation and follow-up of women treated in this way were undertaken.

In the meantime, it might be illuminating to survey GPs regarding their attitudes to HRT prescription in the light of their perceptions of high and low risk factors in menopausal women. Similar studies in the US have proved

to give interesting insights, for example, the risks associated with the development of osteoporosis did not influence physicians' judgements about prescription practice when presented with patient case descriptions, despite the fact that the physicians did recognise the ability of HRT to reduce such risks (Holzman et al., 1984).

6. Closer scrutiny of the health care resources actually used by women in the UK who take HRT is desirable if the total costs of HRT use rather than merely the prescription costs, are to be detailed.

7. In general terms it is evident that information which could be obtained from case-control and cohort studies relating to currently acceptable doses, duration of use, types of preparation and methods of administration would not be available immediately due to the lag between use and effects on some conditions. However, what is important is to recognise that, unless research is initiated now then opportunities will be lost and useful data will be even less available in the future. The identification and matching to controls of women who have begun to use more recent types of therapy is therefore essential and is a priority issue if good quality information is to be gained.

In conclusion, there is a major need to begin to focus on the setting up of new research to produce good medical evidence about the risks and benefits associated with the use of the currently acceptable forms of HRT used in the UK. However, as with all rapidly changing health care strategies, new developments are likely to occur which will make even relatively recent evidence outdated. Detailed evidence regarding long-term risks and benefits can obviously only be gained after considerable duration of use and therefore will again suffer from being inapplicable to future prescribing patterns.

Perhaps of more immediate importance is the requirement to elicit women's valuations regarding the impact of HRT use on their quality of life and how this influences their attitudes to the relative risks that might be associated with HRT use. Using trade-off techniques to obtain quantitative information, it might then be possible to begin to produce estimates of the "quality adjusted" effects of HRT use. As the "benefit" of the equation will be heavily influenced by quality effects, the need for such research is obviously urgent and will be of great importance for future analyses of HRT use.

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