Use of hormone replacement therapy

Evidence on risk of breast cancer associated with hormone replacement therapy is still inconclusive

EDITOR,—As a female doctor who has a specialist interest in the menopause and hormone replacement therapy, I was interested to read Elizabeth H Price and Helen Kaye Little's letter about hormone replacement therapy.¹ I agree that women need to be informed about the risks associated with such treatment. I disagree, however, with the authors' statements about the increased risk of breast cancer.

The epidemiological evidence on the effect of combined treatment with oestrogen and progestin on the risk of breast cancer is still too limited to be conclusive: neither a protective nor a detrimental effect has been reliably shown. The largest case-control study (from the Centers for Disease Control²), the largest cohort follow up study (the nurses' health study³), and the most recent case-control study⁴ failed to find a link between breast cancer and use of oestrogen up to 20 years. Lower doses of oestrogen, which protect against osteoporosis and cardiovascular disease, are not known to be associated with an increased risk of breast cancer. A recent meta-analysis detected a small increased relative risk of breast cancer being diagnosed in women taking combined oral contraceptives.⁵ This study, however, was not free of selection and detection bias or of the risk of a positive result emerging owing to the heterogeneity of the studies included. Only a randomised clinical trial will provide definitive information on this issue.

It is my practice to give patients evidence based information about the risks and benefits of hormone replacement therapy. The evidence overwhelmingly supports the protective effects of such treatment on the cardiovascular system and against osteoporosis; it remains equivocal on the risks of breast cancer. I do not believe that it is appropriate to make either positive or negative statements about the effects of hormone replacement therapy on health on the basis of single references, as Price and Little do. No treatment is without risk, and I regard my patients as responsible adults who will make their own decisions on the basis of the best information I can provide. I encourage the provision of information by groups such as DASH (Doctors Against Abuse from Steroid Sex Hormones)¹ if that information is complete and unbiased.

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May depend on whether the menopause is regarded as physiological or pathological

EDITOR,—Elizabeth H Price and Helen Kaye Little voice concern about the "considerable pressure" that may be exerted on women to use hormone replacement therapy.¹ The perceived risks and benefits should be fully discussed with each woman so that she can make an informed choice. Whether a doctor promotes the use of such treatment for asymptomatic women is likely to depend on his or her philosophical view of the menopause as either a physiological or a pathological state.

Price and Little consider the menopause to be physiological and hormone replacement therapy to be a drug that should not be offered to a general population. This view requires the belief that an event that potentially affects all women must be part of the normal aging process. This fact alone is not irrefutable evidence that the menopause is a physiological process. This century, average female life expectancy has risen from 45 to 83 years. This is almost entirely related to considerable improvements in social conditions and means that a woman may now spend almost one third of her life in the postmenopausal state. If we look at other mammals we find that reproductive capacity is maintained until death. Perhaps we can regard the menopause as the onset of a pathological state to which women are exposed only because of socially induced longevity.

Overall, epidemiological studies have shown low dose natural oestrogen to have significant

protective effects against cardiovascular and cerebrovascular disease (major causes of death in our society). Continuing research suggests a protective influence in Alzheimer's disease.² The risk of breast cancer remains uncertain, with two recent reports coming to opposite conclusions.^{3,4}

Price and Little refer to a paper by Hunt *et al.*,⁵ quoting a 50% increase in the risk of breast cancer with use of hormone replacement therapy for more than five years. This is exactly the sort of selective quotation that must be avoided. They fail to highlight the fact that use of hormone replacement therapy was associated with a significant reduction in all cause mortality (relative risk 0.56 (95% confidence interval 0.47 to 0.66)), including all deaths related to cancer (0.70 (0.55 to 0.85)).⁵

In promoting hormone replacement therapy we should all endeavour to explore the potential benefits, risks, and uncertainties with women, helping them to reach their own conclusions. Organisations such as DASH (Doctors Against Abuse from Steroid Sex Hormones)¹ are one source of information; I hope that DASH will offer counselling that is both balanced and evidence based.

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Authors gave distorted view through selective citation

EDITOR,—What women most certainly do not need is Elizabeth H Price and Helen Kaye Little's highly selective citation of the literature.¹ The authors refer to an editorial by McPherson, which stated that five years' use of hormone replacement therapy is associated with a 50% increase in the risk of breast cancer.² They express surprise that research in which McPherson participated should have found that 55% of postmenopausal female doctors choose nevertheless to take hormone replacement therapy.³ They explain this figure as being the result of "considerable pressure [on women] to use hormone replacement therapy." This implies a contempt for their female colleagues, which would rightly be condemned as sexist and patriarchal if it originated from a male doctor.

McPherson's editorial drew heavily on the latest report from the nurses' health study,⁴ in which women who had stopped taking hormone replacement therapy two years previously were found to be at no higher risk of breast cancer, regardless of the duration of use, than women who had never used it. In the Iowa women's health study mortality from breast cancer was increased by 45% in

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women using hormone replacement therapy for up to five years but was not significantly increased in women using it for longer.⁵ Neither of these observations is consistent with a causal relation between sex steroid hormones and cancer, such as that so clearly shown between unopposed oestrogens and endometrial cancer. Price and Little also completely ignore a recent population based case-control study that showed no increase in the risk of breast cancer even when hormone replacement therapy was taken for 20 years and more.⁶

While relying uncritically on the report on use of hormone replacement therapy and breast cancer from the nurses' health study, the authors perfunctorily dismiss the finding from the same cohort of a 50% reduction in the risk of myocardial infarction among women using the therapy. We recognise that epidemiology has provided no easy answer to the question of whether use of hormone replacement therapy has an effect on the risk of breast cancer, but we object to the promulgation of any attitude towards hormone replacement therapy, whether positive or negative, that is based on prejudice and a personal agenda. Making an announcement of a new organisation is no excuse for such abuse of the literature. Sadly, it is all too easy for those with no clinical responsibility for hormone replacement therapy to present a distorted view, to the detriment of women seeking a balanced assessment of the benefits and risks.

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Hormone replacement therapy may not always be right choice to prevent cardiovascular disease

EDITOR,—Hormone replacement therapy in postmenopausal women has been shown to have an overall benefit on mortality.^{1,2} None of the studies, however, were carried out in countries with a low frequency of ischaemic heart disease; nor were trends in mortality taken into account.

We performed a risk-benefit analysis of the effect of hormone replacement therapy on mortality from ischaemic heart disease, breast cancer, stroke, and endometrial cancer in postmenopausal women. Reference mortalities were estimated for successive birth cohorts of Italian women by age range, and a cohort log linear regression model was fitted to corresponding cause specific mortality data.³ Mortalities achievable with mass treatment were estimated by multiplying the reference mortalities by the relative risks derived from the literature.^{1,2,4,5} Italian

Fig 1—Trends in mortality from breast cancer, ischaemic heart disease, and stroke among female birth cohorts in Italy

women were assumed to start taking oral hormone replacement therapy (combined oestrogen and progestin) at age 50 and to continue it for 10 years. No risk or benefit was expected in the first five years of treatment. The benefit for ischaemic heart disease after the start of hormone replacement therapy was assumed to be 0.88 after five years, 0.75 between 10 and 15 years, and 0.88 between 15 and 20 years; the risk for stroke was assumed to be 0.88 between five and 20 years; the risk for breast cancer was assumed to be 1.2 after five years and 1.46 between 15 and 20 years; and no risk or benefit was applied for endometrial cancer.

Oral hormone replacement therapy for 10 years was estimated to produce an overall disadvantage in terms of life expectancy: we estimated that 59 and 62 excess deaths would occur between the ages of 50 and 70 in 100 000 Italian women born in 1940 and 1950, respectively.

This risk-benefit analysis is the first to have been conducted in a country with a low incidence of ischaemic heart disease and that is experiencing a steep decrease in mortality from cardiovascular disease in successive birth cohorts (fig 1). The result suggests that caution is necessary when oral hormone replacement therapy is envisaged as a tool for mass primary prevention of cardiovascular disease in postmenopausal women. This is particularly the case in populations at low risk of ischaemic heart disease, with higher mortality from breast cancer than from ischaemic heart disease before age 60, and with a decreasing trend in mortality from cardiovascular disease, as in other European countries such as France and Spain.

This study was supported by the Italian National Research Council and the Italian Association for Research on Cancer.

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Modes of administration of morphine in cancer pain

Some doctors lack basic knowledge about prescribing morphine

EDITOR,—The use of morphine is still associated with unfounded fears, even though the modern hospice and palliative care movement has existed for almost 30 years. Hopefully, the explicit guidelines on the use of morphine for cancer pain drawn up by the Expert Working Group of the European Association for Palliative Care will help dispel these fears.¹

Certain concerns are legitimate. A particular worry is the lack of individualisation of both the starting dose of morphine and the continuing dose, especially in patients who have not taken morphine before. Age, frailty, and known or possible renal impairment are often not considered. Twice in recent months we have admitted elderly patients (aged over 80) who had been given an excessive dose of analgesic cover "for the journey"; they had never previously been given morphine. One had been given 10 mg of diamorphine subcutaneously (equivalent to 30 mg of immediate release morphine), while the other had been given 20 mg of immediate release oral morphine. On arrival both patients were heavily sedated, with diminished respiratory drive. Probably a dose of only 2.5 mg of immediate release oral morphine would have sufficed.

Another area for potential mismanagement is when patients are changed from oral morphine to subcutaneous diamorphine given by syringe driver. We recently saw a patient who had been taking a total of 80 mg of controlled release oral morphine daily and had been changed to a syringe driver with 120 mg of diamorphine in 24 hours (equivalent to 360 mg of oral morphine daily). A dose of 25 mg of diamorphine in 24 hours by syringe driver was sufficient.

Doubtless most doctors try to use morphine in a considered manner, but, as is shown above, some have a worrying lack of basic knowledge. Continued reiteration of basic guidelines is essential.

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Formulations of morphine sulphate are easily confused

EDITOR,—The recommendations for the use of morphine in cancer pain produced by the Expert Working Group of the European Association for Palliative Care provide a comprehensive framework that will be of benefit to all health care professionals caring for this group of patients.¹ Prescribing morphine sulphate may, however,