

Menopausal Hormone Therapy

Fracture protection mediated through the brain?

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KEY POINTS

- Because the majority of fractures occur in individuals without osteoporosis it is apparent that bone mass is not the only determinant of fracture risk.
- Postural imbalance increases a woman's risk of falls and fractures; postural balance is known to deteriorate with age.
- Data from hormone therapy studies indicate that low levels of estradiol have negative effects on postural balance.
- Improvements in postural balance may explain the rapid beneficial effect of hormone therapy on hip fractures after therapy is started and the quick disappearance of benefit when therapy is discontinued.

The high incidence of fracture in elderly individuals is a matter of concern; research into the reduction of fracture risk in this age-group has historically focused on the perceived need to preserve or increase bone mass. However, the cost of medical interventions to this end has been estimated to be almost as great as the cost of treating the fractures. Further, peripheral bone mass measurements have indicated that more than 80% of postmenopausal women with fractures do not have osteoporosis; in fact, more than 90% of all hip fractures result from a simple fall. Research also has revealed that after medical intervention for low bone mass, there is a poor correlation between in-

creased bone mass and reduced risk of peripheral fractures.

These seemingly paradoxical findings have stirred interest in recent data suggesting that the fracture-protective effect of menopausal hormone therapy (HT) might be partly mediated through effects on the brain, with subsequent improved postural balance and fewer falls.

Increasing burden of hip fracture

The number of elderly individuals is steadily increasing all over the world, partly because of the increase in life expectancy in many countries. In Europe, the number of individuals aged 65 years and older is expected to increase from about 69 million in 1990 to more than 133 million in 2050, and in Asia, this number will grow from 145 million to 894 million. This increase alone could cause the number of hip fractures in the world to increase from 1.7 million in 1990 to more than 6 million in 2050, with most of the fractures occurring in

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FROM THE EDITOR



The current issue of Menopausal Medicine

contains 2 disparate but interesting articles on the use of estrogen therapy (ET) or estrogen plus progestin therapy (EPT) in postmenopausal women. The role of ET for prevention of hip fracture presents a unique discussion of the mechanisms involved in hip fracture reduction. The reduction in hip fracture may not be a simple increase in bone mass but, more important, it could be related to improved central nervous system (CNS) activity. The association of neoplasia of the breast, uterus, and ovary with the use of ET or EPT is reviewed using current data to provide the background for decision making.

The cause of most hip fractures is trauma from a fall. Tord Naessen, MD, PhD, presents data on the role of estrogen in preventing postural sway as a potential mechanism that results in a reduction in hip fracture among aging women. The rapid onset of protection against hip fracture with the use of hormone therapy (HT) and the equally rapid loss of protection with discontinuation of HT supports his proposition that bone mass alone is not a significant protection for women with low bone mass. His data on the prevention of postural sway during aging with estrogen provide a compelling case that CNS involvement is important in reducing falls and their sequelae.

The finding of no effect of ET on postural sway in older women who have not previously used HT supports the current hypothesis of a "window of opportunity" for the use of estrogen in the early postmenopausal woman. This hypothesis implies that continuation of HT after menopause for a variable time period may reduce the development of disease. Suggestive evidence for this finding in the CNS was found in the Cache County study that early use of estrogen compared with later use reduced the relative risk of Alzheimer's disease. These and other data are provocative regarding this hypothesis and need further study to clearly delineate the importance of HT in the early postmenopausal woman.

Rod Baber, MD, BPharm, provides information regarding the use of ET or EPT and the development of neoplasia of the breast, uterus, and ovary that can be used for counseling. This discussion centers on the magnitude of the relative risk and the actual attributable risk presenting the number of cases above the background incidence with use of HT. The emphasis is on breast cancer, and the point is made that the data show a relatively weak association with low attributable risk for EPT and breast cancer. This is not the case with ET and endometrial cancer, in which ET is shown to increase proliferation, hyperplasia, and neoplasia. The addition of the progestogen reduces the incidence of endometrial cancer to that present in women who had never used ET. Overall, an increase in ovarian cancer does not appear to be associated with the use of ET or EPT, although the data are mixed. Cervical cancer is not associated with the use of HT.

The ultimate decision to use ET or EPT is made in consultation between the patient and the physician. Knowledge of the data included in the article by Dr Baber is important in counseling because of the differences in outcomes for breast, endometrial, and ovarian cancer. It is important to reiterate that these studies, both clinical trials and epidemiologic data, do not provide the final important link of causation for hormones and neoplasia. The data from population studies are important, but the applicability of this information to the individual patient requires the health care provider's knowledge of the data and the individual patient's risk factors. The ability to clearly formulate the potential risk for the individual patient constitutes the practice of medicine.

David F. Archer, MD

Asia.¹ This article discusses the relevance of low bone mass and falls to the occurrence of hip fractures in elderly individuals. In addition, it discusses how the relative importance of these factors changes with aging and the effects of interventions for reducing fracture risk.

Bone mass: Decreasing importance with age

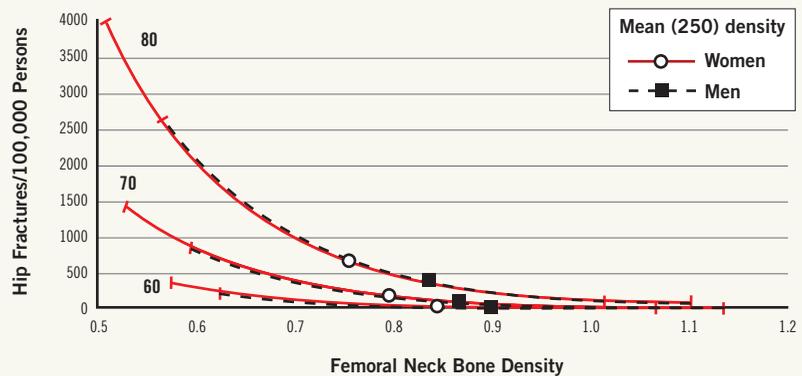
Bone mass is strongly associated with fracture risk, especially in women aged 65 years and older.² Bone mass decreases in both sexes with aging, and the risk of osteoporotic fractures in women doubles every 7 or 8 years after age 50 years.² Because women start with lower bone mass and have greater bone loss and more falls than men, the incidence of hip fracture is twice as high in women as it is in men. In addition, women live longer than men, which means that as many as three-quarters of the total number of hip fractures occur in women.¹

Nevertheless, it has been demonstrated that the risk of fracture varies considerably in different age ranges despite similar bone mineral density (BMD) values.³ FIGURE 1 shows that the relation between hip fracture and bone mass weakens with age. In this study by de Laet et al, only 13% of the increase in hip fracture risk from age 60 to 80 years was attributable to a decrease in bone mass.³ Thus, the relative importance of bone mass as a cause of hip fracture decreases with increasing age³ and other factors become more important.

Although low bone mass is associated with an increase in fracture risk, the vast majority of fractures in elderly individuals occur in people without osteoporosis. In the Study of Osteoporotic Fractures (SOF), 80% of all fractures occurred in

FIGURE 1

Fracture risk based on age and bone mineral density



One-year cumulative incidence of hip fracture versus femoral neck bone density at ages 60, 70, and 80 years in women and men.

Adapted with permission from de Laet CE, et al. *BMJ*. 1997;315:221-225.

people with “normal” peripheral bone mass (ie, no osteoporosis).⁴ Similarly, in the Rotterdam study, more than half of the nonvertebral fractures occurred in women without osteoporosis, as assessed by dual energy X-ray absorptiometry measurements of the femoral neck.⁵ Thus, although the rate of fracture may be greater in women with osteoporosis, the majority of fractures occur in people without osteoporosis. Therefore, other contributing factors have to be taken into account, such as those recently reviewed in this newsletter by Dr Goldstein.⁶ This short review discusses some of the relevant facts, with particular reference to postural balance and falls, which are important causes of hip fracture in elderly people.

Multifactorial genesis of falls

Fractures in elderly people, especially peripheral fractures such as distal forearm fractures and hip fractures, have a clear multifactorial genesis. Along with decreased BMD, poor postural balance and falls are important causes of peripheral fractures. Approximately

30% of community-dwelling individuals older than 65 years fall each year; a fifth of these falls require medical attention.⁷ About 90% of hip fractures in both sexes result from a simple fall¹ and the importance of the fall as a cause of hip fracture increases with aging.

In women, the risk of distal forearm fracture increases sharply around the time of menopause, in parallel with an increase in reported falls.⁸ It has been suggested that these rapid changes are linked with falling serum estrogen levels during the menopausal transition.⁸

Postural balance deteriorates exponentially with aging in both sexes, and it is also well known that the balance function can be negatively affected by medications such as sedative-hypnotic drugs, resulting in an increased fracture risk. Impaired postural balance is increasingly related to the occurrence of falls and hip fracture as an individual ages.

Interventions to reduce the number of fractures

During the last few decades, considerable effort has gone into find-

TABLE

Effect of hormone therapy on fracture risk by age at start of therapy

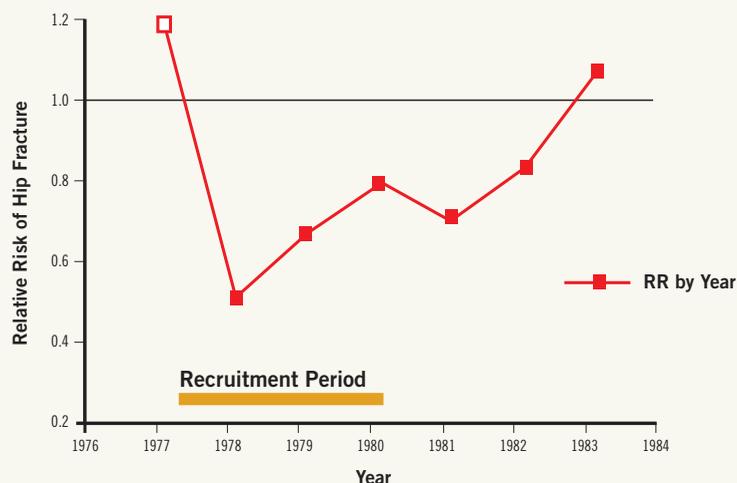
| Type of Fracture | Age at Start of HT | Relative Risk |
|------------------|--------------------|-----------------|
| Hip and wrist | <60 y | 0.45 (0.3, 0.8) |
| Hip and wrist | >60 y | 0.88 (0.5, 1.6) |

Meta-analysis based on 14 trials.

Torgerson DJ, Bell-Syer SE. *JAMA*. 2001;285:2891-2897.

FIGURE 2

Hip fractures during and after hormone therapy



Relative risk of hip fracture in 23,000 women during and after a period of receiving prescriptions for hormone therapy (HT). Questionnaires filled out by participants indicated that only 20% were still using HT at the end of follow-up (1983).

Adapted with permission from Naessen T, et al. *Ann Intern Med*. 1990;113:95-103.

ing agents to reduce bone loss and increase bone mass. It has been estimated that the costs of these medical interventions could be as great as the cost of treating the fractures.

Effects of medical interventions

Although agents used to increase bone mass may have similar effects on this parameter, they can have quite different effects on the risk of peripheral (distal forearm and hip) fractures. Commonly used agents that preserve or increase bone mass include estrogen HT, bisphosphonates, and the selective estrogen receptor modulator raloxifene.

HT and bisphosphonates increase bone mass to a roughly com-

parable extent; raloxifene is about half as effective. HT, bisphosphonates, and raloxifene are also fairly comparable with regard to reducing the risk of vertebral fracture. However, when we look at the risk of peripheral fractures such as those of the hip or distal forearm, a different picture emerges.

Modern agents such as raloxifene substantially reduce the risk of vertebral fractures in osteoporotic women but often have substantially less or virtually no effect on the risk of hip fracture (relative risk, 0.90), despite the large number of elderly subjects studied.⁹ Similarly, when the bisphosphonate alendronate is given soon af-

ter menopause,¹⁰ BMD is increased to a similar extent to that reported after HT but the reduction in hip fracture risk is often smaller. Admittedly, differences in age and degree of osteoporosis in the various studies may explain some of these findings. However, if decreased BMD were the basis for increased peripheral fractures in the elderly, the magnitude of increase in BMD after bisphosphonate therapy should have a more substantial effect on the risk of peripheral fractures than is actually seen.

In contrast to the effects of these agents, postmenopausal HT has been shown to rapidly and substantially reduce the risk of forearm and hip fractures in numerous reports during recent decades.¹¹⁻¹³ Interestingly, the rapid reduction in hip fracture risk is often reported in the period soon after menopause, when bone mass in general is still fairly "normal." In fact, this fracture risk is not substantially different from that of premenopausal women, that is, in women who are at low risk of fracture (TABLE).^{12,14}

Adjusting environmental factors to reduce risk

Certain environmental interventions can reduce the number of falls, especially when applied individually or in institutions. The effects of these interventions on fracture risk are currently unclear.⁷ Thus, it is estimated that multiple risk factor interventions could reduce the risk of falling by about 23%, but there seem to be only modest effects on reducing the risk of fracture.⁷

Hip protectors. Studies on the effect of hip protectors show some effect in reducing the risk of hip fracture in institutions, but the data are not convincing and there is no evidence of benefit for the majority of older

people living in their own homes.¹⁵ **Regular physical exercise.** It is generally agreed that regular weight-bearing exercise has a positive effect on the musculoskeletal² and neuromuscular systems. Physical activity has little effect on bone mass, but it has been associated with reduction of fracture risk,¹⁶ most likely through a reduced tendency to fall, achieved by training the neuromuscular system.

Interestingly, in the Nurses' Health Study, the effect of HT on hip fracture risk was more pronounced in women with a low rating for physical activity than for those with a higher physical activity rating.¹⁷ This finding suggests that HT and physical activity could share a similar mechanism in reducing the risk of fracture. It is tentatively suggested that this mechanism could revolve around improved postural balance.

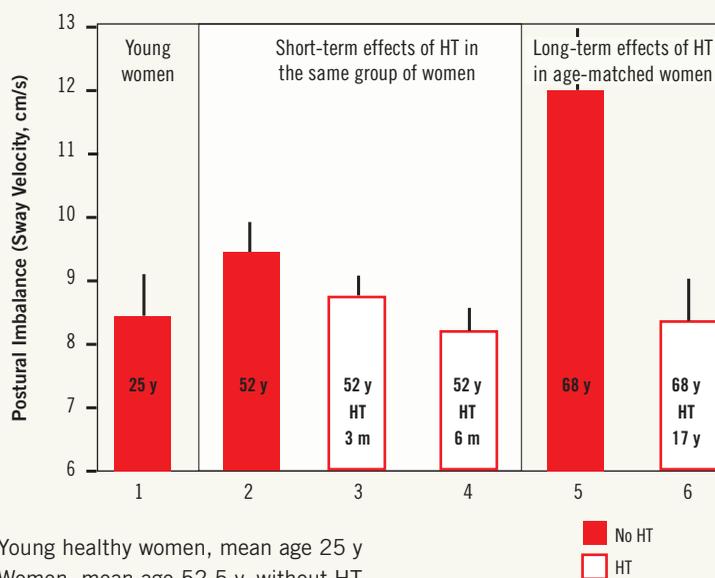
Postural balance: Mediating fracture risk

When HT is initiated soon after menopause, the risks of falls,¹⁸ fractures in general, and distal forearm fractures in particular¹¹ are reduced. In our cohort study, the reduction in the risk of hip fracture seemed to occur immediately after initiation of HT and to wear off rapidly after withdrawal of HT, seemingly too rapidly to be explained by preservation of bone mass alone (FIGURE 2).¹²

A similar rapid start and disappearance of the effects of HT on hip fracture risk has also been reported by Cauley et al¹³ and in a recent report based on the Million Women Study.¹⁹ Our data also indicated that the effect on the risk of hip fracture was greater when HT was initiated sooner rather than later after menopause (ie, before

FIGURE 3

Postural balance after short-term and long-term HT



1. Young healthy women, mean age 25 y
2. Women, mean age 52.5 y, without HT
3. Same women as column 2 after 3 months of HT
4. Same women as column 2 after 6 months of HT
5. Women without HT, mean age 68 y, age-matched to women in column 6
6. Women with HT since menopause, mean duration 17 y

HT, hormone therapy.

Postural balance in women at various mean ages and the short-term and long-term effects of HT initiated soon after menopause.

Adapted from Naessen T, et al. *Menopause*. 2007;14:14-19.

rather than after age 60 years).¹² This greater reduction in the risk of hip fracture when HT is initiated soon after menopause has been confirmed in a meta-analysis of 14 randomized studies (TABLE).¹⁴

These findings may seem surprising and paradoxical, considering that bone mass is almost normal at menopause and that the increase in bone mass when HT is initiated in elderly people with lower bone mass is generally greater than that when HT is initiated closer to menopause. However, these findings support the concept that factors other than bone mass provide a protective effect against hip fracture.

Low bone mass and falling have previously been the focus of attention with respect to the occurrence of hip fracture. However,

with increasing age, postural balance also deteriorates, thus increasing the risk of falls and fracture.

HT and postural balance: The data

It is a well established fact that postural balance deteriorates with aging. FIGURE 3 shows postural balance values in women with mean ages of 25, 52, and 68 years. We recently reported that 6 months of HT initiated soon after menopause rapidly and significantly improved postural sway, as assessed on a sway platform. In this group of women, the mean age was 52 years, and postural sway levels were equivalent to levels normally seen in young healthy women between 20 and 30 years of age.²⁰ In addition, estrogen therapy started at the time of

menopause and continued into old age seems to preserve postural sway at values similar to those in young healthy women and substantially better than those in age-matched postmenopausal women.²¹

On the assumption that deterioration in postural sway is associated with an increased propensity for falling, these findings could suggest that the improved postural balance seen with HT might contribute to the observed protection against peripheral fractures associated with HT. Further, it could also explain the rapid and more substantial reduction in risk of hip fracture when HT is initiated sooner rather than later after menopause.

Unpublished data indicate that when HT was initiated later (after age 60 years), postural balance was significantly improved in women with low serum estradiol (E2) levels at baseline. In women on placebo, subtle differences in baseline serum E2 levels seemed to be important for the rate of change in postural balance during the study. Low baseline endogenous serum E2 levels were associated with a greater deterioration of postural balance during the study than higher serum E2 levels, although all levels were within the normal postmenopausal range for estradiol.

The effects of HT on postural balance appeared to emerge more slowly than the effects seen in women receiving HT soon after menopause.²⁰ Thus, substantial improvements in postural balance could require longer than 6 months of HT if the therapy is initiated later after menopause.

An increased fracture risk was recently reported in postmenopausal women with low endogenous serum E2 levels.²² One could speculate that the increased fracture risk in these women could be

a composite result of lower BMD and the negative effects of low serum E2 levels on postural balance. In fact, the results from our studies are all consistent with the “critical window” hypothesis of more beneficial effects of HT when therapy is initiated soon after menopause.

“Critical window” hypothesis

The critical window hypothesis states that the effects of HT, including those on the human brain, are more beneficial if HT is initiated sooner rather than later after menopause.²³ Interestingly, in the large observational SOF (mean age 70 years), current estrogen therapy had no substantial effects on muscle strength and neuromuscular function.²⁴ However, in the same study, women who had started HT soon after menopause and then discontinued use had significantly higher gait speed and better balance than women who had never used estrogens.²⁴ This finding also fits with the critical window hypothesis.

Our results indicated that low serum E2 levels and longer time since last menstrual period (longer duration of low E2 levels) had negative effects on postural balance. More rapid and substantial improvements in postural balance were seen when HT was initiated sooner rather than later after menopause.²⁰

Our findings, and some of the results of the SOF, are totally consistent with the critical window hypothesis, that is, that estrogen exposure soon after menopause might have positive effects many years later in life.

Summary

The development of agents for protection against fractures has historically focused on the per-

ceived need for preservation of or increase in bone mass. However, the majority of hip fractures occur in individuals without osteoporosis. There are probably few hips that will withstand the high energy released from the type of fall that occurs in elderly people, a lateral-backward fall, directly onto the hip, irrespective of the BMD of that hip. The risk of fracture is far from only a question of bone mass.

The potential effects of HT on the brain, the overall orchestrator of human activities, including postural balance, could explain some of the rapid changes in fracture risk seen in association with HT use and the greater reductions in hip fracture risk when HT is initiated sooner rather than later after menopause. Brain function is affected by normal aging as well as by certain types of medical interventions. The negative effect of sedative/hypnotic drugs on postural balance and the resulting increase in fracture risk is well known.

Commonly used drugs for reducing fracture risk seem to differ in efficacy for peripheral fractures. Differences in the effects on the brain and postural balance could be one reason for the often greater effects of HT on peripheral fracture risk, compared with the effects of nonhormonal agents such as bisphosphonates.

With increasing age, the importance of low bone mass as a cause of hip fracture seems to diminish and that of postural balance and falls seems to increase. Medical interventions appear to differ in their effects on postural balance. Therefore, pharmaceutical agents aiming to reduce fracture risk by maintaining or increasing bone mass should also improve postural balance, in order to obtain optimal effect in reducing the risk of hip and distal forearm fractures.

Disclosure

The author revealed the following potential conflicts of interest: Member of scientific advisory board, NovoNordisk and Organon AB, Sweden; receives honoraria for lectures.

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Hormone therapy and breast, ovarian, and endometrial cancer

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The alarm generated by the publication of the results from the first arm of the Women's Health Initiative (WHI) randomized clinical trial¹ in July 2002 led many women to cease using hormone therapy (HT). In the United States, HT use dropped by 37%; similar reductions were seen in Australia, the United Kingdom, and Europe.²

The major reason given for cessation of HT was the fear of

cancer, particularly breast cancer. Although studies in recent times have sought to provide reassurance to patients and clinicians alike, the perception still exists in many quarters that HT for the alleviation of menopausal symptoms, even in the short term, is too dangerous a course to follow.

The publication, in the past year, of follow-up data from the WHI³ and the Nurses' Health Study,⁴ among others, have provided extra information with which to accurately assess the relation of postmenopausal hormone use to the risk of gynecologic cancers.

Breast cancer: Low absolute risk

Breast cancer is the most common cancer in women. The incidence varies among communities; it is higher in developed Western countries and lower in Asian countries.

A link has been well established between endogenous hormones and breast cancer risk. Larger numbers of ovulatory cycles are associated with an increased risk of breast cancer, for example, in women who have an early menarche, a late menopause, or fewer pregnancies. Postmenopausal women with high-

er bone density, and, on average, higher levels of endogenous estrogens, are known to have a higher breast cancer risk than do their low-bone-density peers.

Drugs that block the effects of endogenous estrogen, such as the selective estrogen receptor modulators tamoxifen and raloxifene, reduce the risk of breast cancer in high-risk women. The use of tamoxifen and raloxifene in the NSABP P-1 Trial⁵ and the STAR Trials⁶ has been shown to reduce the risk of breast cancer in high-risk populations. Similarly, aromatase inhibitors have been shown to reduce the risk of recurrent disease in postmenopausal women with estrogen-receptor positive breast cancer,⁷ as has prophylactic bilateral oophorectomy.

Observational studies

The proposition that postmenopausal hormones might increase the risk of breast cancer was not new to the WHI. Observational studies of varying quality had reported increased risks for approximately 20 years prior to the publication of WHI. One large, long-running observational study, the Nurses' Health Study,⁸ reported a 1.46 relative risk (RR) of breast cancer for users of HT of more than 5 years' duration.

A collaborative reanalysis of the medical literature⁹ reported similar results of an RR of 1.35 after more than 5 years of HT use. The collaborative reanalysis included 52,705 women with breast cancer and 108,411 without. Of these, 40% were premenopausal, 42% were postmenopausal, and the median age at their menopause was 50 years.

Among nonusers of HT, postmenopausal women had a lower risk of breast cancer than

KEY POINTS

- Absolute changes in gynecologic cancers due to use of hormone therapy are very small.
- The increase in breast cancer among women who use combined hormone therapy is 8 per 10,000 women per year after 5 years of use.
- In spite of inconsistent data, the risk of ovarian cancer appears to increase with estrogen-only therapy. In absolute terms, the increase is 1 additional case of cancer per 10,000 women per year.
- Endometrial cancer rates appear to increase by 12 to 15 cases per 10,000 women per year with estrogen-only therapy; this risk is negated when a progestin is added to the regimen.

did premenopausal women of the same age, suggesting a protective effect of estrogen withdrawal.⁹ The RR increased by 2.8% for each year that menopause was delayed. Once menopause had occurred, the RR decreased by 2.7% for each year thereafter. This reduction in risk was greater for women with a lower body mass index (BMI), perhaps because of greater peripheral conversion of adrenal androgens to estrogens in adipose tissue of women with a higher BMI. Postmenopausal risk increased by 3.1% with each kg/m² increase in weight after the menopause.

Among users of HT in the collaborative reanalysis,⁹ no significant increase in breast cancer was seen for 4 years of HT use. However, for 5 to 9 years of use, the RR was 1.31 and it increased to 1.56 after 15 years or more of use.

The first WHI data

The data in collaborative reanalysis⁹ are broadly consistent with the data from the WHI estrogen and progestin arm published in 2002.¹ In this randomized clinical trial involving 16,608 women with an intact uterus randomized to placebo or conjugated equine estrogen (CEE), 0.625 mg, plus medroxyprogesterone acetate (MPA), 2.5 mg daily, there was an increased risk of breast cancer; the hazard ratio of 1.26 (1.00-1.59) just failed to reach statistical significance.

The increase in breast cancer was first seen in year 4 and was seen only in previous users of HT. For new users of HT in the WHI trial, there was no statistically significant increase in the risk of breast cancer for the duration of the study, which suggests that there is a safe "window of opportunity" of up to 5 years for HT use to alleviate menopausal symptoms.

Tumor grade was the same in both arms of this study, tumor size was larger in the treatment group than in the placebo group (1.7 vs 1.5 cm), and node involvement was greater in the treatment arm (25.8% vs 15.9%). Mammographic abnormalities and an increase in mammographic density were more common among users of continuous combined HT. A post hoc analysis of the first WHI paper after 6 additional months of follow-up¹⁰ confirmed these findings with a statistically significant RR of 1.24 (1.02-1.50).

Estrogen-only therapy in the WHI

In April 2004, data from the estrogen-only arm of the WHI trial were published.¹¹ In this trial of 10,739 women, including 237 women with invasive breast cancer, there was no increase in the risk of breast cancer for users of CEE alone. Indeed, the hazard ratio of 0.77 (0.59-1.01) came close to a statistically significant reduction in risk.

A follow-up publication of this paper in 2006 reported a hazard ratio of 0.8 (0.62-1.04) for invasive breast cancer, which again was not statistically significant.³ However, for ductal carcinoma, the most common type of breast cancer, the reduction in RR of 0.71 (0.52-0.99) was statistically significant. Mammographic abnormalities were increased in the treatment group compared with placebo, with rates of 9.2% versus 5.5%, respectively, after 1 year, rising to cumulative levels of 36.2% versus 28.1% at the conclusion of the trial.

As well as the intention-to-treat analysis, this paper published data from an adherence-adjusted model including only women who had taken at least 80% of their study medication for the duration of the trial. In this model, the RR of

TABLE

Risk factors for breast cancer

| | |
|------------------|--|
| RR 1.26 | if HT >5 y |
| RR 1.2–1.5 | if menarche <12 y |
| RR 1.37 | if lack of breastfeeding |
| RR 2.0 | if weight increase >20 kg in postmenopause |
| RR 2.0 | if alcohol is consumed |
| RR 2.0 | if age at menopause >55 y |
| RR 2.6 | if family history of breast cancer |
| RR 2.8 (1.9-3.5) | if late birth, >30 y |
| RR 7.0 | if high breast density |
| RR 32 | if DES vaginal cancer |
| RR 60 | if smoking for lung cancer |

DES, diethylstilbestrol; HT, hormone therapy; RR, relative risk.
Ursin G, et al. *Cancer*. 2004;101:353-362.

breast cancer was 0.67 (0.47-0.97), a statistically significant reduction.

Estrogen-only data from the Nurses' Health Study

The Nurses' Health Study investigators⁴ also published follow-up data in 2006 that showed that the effect of estrogen-only therapy (ET) on breast cancer risk was much less than the effect seen with combined therapy. The risk of breast cancer among users of ET was significantly increased only after 20 years of therapy (RR 1.42 [1.13-1.77]), and the risk of estrogen-receptor and progesterone-receptor positive breast cancer among current users of ET was increased after 15 years of use (RR 1.48 [1.05-2.07]).

Bottom line: Breast cancer rates with combined HT versus ET

Early observational studies¹²⁻¹⁵ of the effects of HT and ET on breast cancer risk consistently showed

that combined therapy is associated with a greater risk than is ET, findings that are in accord with those of the WHI randomized trials.

Women taking combined HT have a greater increase in mammographic density than women taking estrogen alone. Any increase in mammographic density may lead to both a delay in diagnosis of breast cancer and an increase in reported mammographic abnormalities; however, breast density increase is itself a significant risk factor for breast cancer. The TABLE lists common risk factors for breast cancer.¹⁶

Ovarian cancer: Increased risk with estrogen-only therapy

Ovarian cancer is a heterogeneous group of disorders of ovarian tissue giving rise to malignant change. The incidence of ovarian cancer among women aged 50 to 59 years is 1 to 2 per 10,000 women per year.

The use of oral contraceptives by premenopausal women has been shown to significantly reduce the risk of ovarian cancers for current and former users.¹⁷

The relation of the use of postmenopausal HT to the risk of ovarian cancer is more vexed, with little consistency between studies. A pooled analysis of 12 studies conducted in the United States from 1956 to 1986 found no evidence of an impact of ET on ovarian cancer risk overall.¹⁸ A meta-analysis of estrogen replacement and ovarian cancer¹⁹ showed no significant association between estrogen replacement therapy and ovarian cancer. Similarly, a paper examining HT formulations and the risk of ovarian cancer showed no significant association between HT or ET and ovarian cancer.²⁰

Conversely, a paper examining

the risk of ovarian cancer following HT use in Swedish women found that ever having used ET or sequential estrogen and progestin therapy increased the risk of ovarian cancer (1.43 and 1.78, respectively).²¹ In this study, ever having used continuous combined estrogen/progestin therapy was not associated with any increase in risk.

A cohort study from the breast cancer demonstration detection project²² examined a cohort of 44,241 women with 329 cases of breast cancer. The group of women who had ever used ET showed an RR of 1.6 (1.2-2.0), ET for 10 to 19 years carried an RR of 1.8 (1.1-3.0), and ET for over 20 years, an RR of 3.2 (1.7-5.7). Ever having used estrogen and progestin was not associated with an increase in risk (RR 1.1 [0.64-1.7]), nor was estrogen and progestin therapy after use of ET, with an RR of 1.5 (0.91-2.4).

In a meta-analysis of postmenopausal hormones and ovarian cancer risk, an increased risk of 24% was associated with 5 years of ET and a nonsignificant increase of 13% was found after 5 years of estrogen and progestin therapy.²³ The increased risk was seen only among women with localized disease, which raises the possibility of a diagnosis/detection bias.

Ovarian cancer in the WHI

The WHI trial published data on the effects of estrogen and progestin on gynecologic cancers in 2003.²⁴ The effects of CEE and MPA were studied in 16,600 women for 5.6 years. In this population, there were 20 cases of ovarian cancer in the treatment arm and 12 in the placebo group, giving rates of 42 per 100,000 women-years for HT users compared with 27 per 100,000 women-years for the placebo group. The RR for ovarian

cancer overall was 1.58 (0.77-3.24), and the RR for epithelial ovarian cancer was 1.64 (0.78-3.45). There were no changes in histologic classes or in the stage or grade of tumor; and there was no significant change overall in the risk of ovarian cancer for users of estrogen and progestin therapy. The authors concluded that although there was no significant increase in ovarian cancer, there was a trend toward an increased risk.

Bottom line: No ovarian protection with postmenopausal HT

Given the data, it is clear that postmenopausal HT does not confer the same protection from ovarian cancer as is seen with the combined oral contraceptive pill.

Drawing a line through major observational and randomized trials gives the impression that ET may be associated with an increase in risk of ovarian cancer. The final data from the WHI estrogen-only study should bring some certainty to this question. For combined therapy, there are still insufficient data from quality trials for firm conclusions to be drawn.

Endometrial cancer: Combined HT negates risk

Estrogen is well known to promote endometrial proliferation and thus increase the risk of endometrial cancer. In premenopausal women, the risk of endometrial cancer is associated with prolonged anovulation and, in particular, with polycystic ovarian syndrome. Reports of endometrial cancer associated with postmenopausal ET became widespread in the United States in the 1970s following a period of time in which unopposed ET was regarded as a safe and appropriate treatment.

Endometrial cancer meta-analysis

Grady et al²⁵ published a meta-analysis of the association between HT and endometrial cancer, which showed a dose- and duration-dependent link between ET and endometrial cancer risk. Endometrial cancer risk was doubled in women who had ever used ET, was increased 3-fold among women using therapy for 1 to 5 years, and was increased perhaps 10-fold with lifelong use.

European population-based study

Weiderpass et al,²⁶ found that women who had ever used estrogen replacement therapy had an RR of endometrial cancer of 3.2 (2.8-4.4) and that with use for more than 5 years, the RR was 3.3 (1.6-5.2). In contrast, women who had ever used estrogen and progestin sequential therapy had an RR of 1.3 (1.0-1.7), and women who had used continuous estrogen and progestin therapy experienced an RR of 0.2 (0.1-0.8) for more than 5 years' use.

Data from the PEPI Trial

The PEPI (Postmenopausal Estrogen/Progestin Intervention) Trial²⁷ in 1996 found that 3 years of treatment with various HT regimens resulted in an increase in simple (27.7%), complex (22.7%), and atypical (11.8%) endometrial hyperplasia in women who used unopposed CEE. In contrast, rates of simple and complex hyperplasia were 0.8% in the placebo group and no cases of atypical hyperplasia were seen. Women who used cyclical or continuous estrogen and progestin therapy showed only nonsignificant increases in simple and complex hyperplasia and no atypical hyperplasia.

US population-based studies

Pike et al²⁸ also showed that ET

increased endometrial cancer risk (RR 2.17 [1.91-2.47]), and also found that duration of progestin therapy was important by demonstrating that cancer risk was still increased if progestins were used for fewer than 10 days a month (RR 1.87 [1.32-2.65]), whereas progestin use for more than 10 days a month or continuously in combination with estrogen did not increase the risk of endometrial cancer.

Million Women Study

The Million Women Study²⁹ showed that ET increased the risk of endometrial cancer (RR 1.45 [1.02-2.06]), although there was no change in risk with sequential therapy and there was a statistically significant reduction in risk for users of continuous combined therapy (RR 0.71 [0.56-0.90]).

Endometrial and cervical cancer in the WHI

In their paper about the WHI trial findings of the effects of estrogen plus progestin on gynecologic cancers, Anderson et al reported an RR for endometrial cancer among users of continuous combined therapy of 0.81 (0.48-1.36).²⁴ There was no difference in the stage, grade, or class of tumor at the diagnosis.

Cervical cancer was also examined in this study, and no difference was seen in cervical cancer incidence among the treatment or placebo groups, although mild dysplasia was significantly increased among the treatment group (7.8% in the treatment group vs 5.5% in the placebo group).

Summary

Absolute changes in the incidence of gynecologic cancers influenced by HT are very small. Breast cancer risk is not increased for users

of combined HT for at least 5 years and for users of ET for at least 7 years. In absolute terms, the increase in cancer among combined HT users is 8 per 10,000 women per year after 5 years.

There is insufficient good-quality evidence to implicate HT in the association of ovarian cancer; however, a suspicion exists that ET might be associated with an increased risk, which, if proven, would amount to 1 extra case per 10,000 women per year in absolute terms.

In women with an intact uterus, endometrial cancer will be increased approximately 3-fold with use of ET for 5 years. In absolute terms, this amounts to 12 to 15 cases of cancer per 10,000 women per year. This risk can be negated by the appropriate use of a progestin continuously or cyclically for at least 10 days per month. Studies conducted on an intrauterine device containing depot release of a synthetic progestin have shown it to provide endometrial protection for normally cycling women and for women taking HT.³⁰

Thus, estrogen alone seems safer for the breast but not for the ovary or the endometrium. For the majority of women taking HT for the short-term alleviation of menopausal symptoms, this will be a matter readily managed by the careful choice of the appropriate dose and regimen of HT. For those women who require long-term HT, we must continue to investigate lower doses, new progestins, and new delivery systems to provide safer ways of delivering treatment. Importantly, randomized clinical trials have shown no increase in overall mortality for all HT users.

Disclosure

The author reported the following potential conflicts of interest: Participant in clinical trials sponsored by Wyeth Ayerst; Organon, Inc.; Novartis Pharmaceuticals Corporation; Pfizer Inc; and Novogen.

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