Appendix B: Evidence on Hormone Replacement Therapy and Fractures

B

A small number of studies have examined directly the relationship between use of hormonal replacement therapy and risk of hip fracture (table B-1). These studies, all of which are of observational design, found a lower incidence of hip fracture in estrogen users versus nonusers, although the differences in incidence did not always reach statistical significance.

The largest and most complete study of hormonal replacement therapy and hip fracture incidence was of a cohort of approximately 23,000 users of hormonal replacement therapy from the Uppsala Health Care Region of Sweden (14). The Uppsala Health Care Region comprises six counties and one-sixth of the total population of Sweden. The authors included in the cohort all women living in the region who were age 35 years and older (mean age 53.7 years at study entry) and who filled at least one prescription for a noncontraceptive estrogen-containing preparation between April 1977 and March 1980. HRT users were identified through the region's prescription record database, which includes records of prescriptions filled at all pharmacies within the region. The authors determined the incidence of first hip fracture in this cohort through 1983 by using each woman's unique national registration number to link each woman's prescription record with there-gion's registry of hospital admissions. The mean duration of observation of members of this cohort was 5.7 years.

Hormone use before 1977 and after 1980 was ascertained by mailing questionnaires to a random sample of 735 women from the cohort in 1980 and again in 1984 (14). Nine percent had not taken the prescribed drug, half of the cohort had begun hormone replacement therapy before the beginning of the study period, and the median duration of HRT was approximately 3.5 years. Approximately one third of the HRT users were prescribed a combined regimen of estrogen and progesterone; the other two thirds used estrogen alone.

The incidence of hip fractures in the cohort was compared with that of the background population of women age 35 and older in the region (14). The study demonstrated a statistically significant reduction in risk of hip fractures in users of hormonal replacement therapy (relative risk 0.79). Women who received hormonal replacement therapy with conjugated estrogens or estradiol showed a significantly reduced risk of hip fracture (relative risk 0.70), whereas virtually no protective effect was found in women prescribed estriols, which are much weaker than the conjugated estrogens or estradiol typically prescribed for hormonal replacement therapy in the United States.

The data indicated that the protective effect of the more potent estrogens was concentrated in women who initiated therapy within a decade after menopause (relative risk 0.55 for women less than 60 years of age at initiation of therapy); no significant protective effect of hormonal replacement therapy was found for women 60 years or older at the time of initiation of therapy (14). However, the data may not be sufficient to indicate whether hormonal replacement therapy has a protective effect for older women because of the relatively small number of cohort members greater than 60 years of age, and the relatively few older members of the cohort who were prescribed the more potent estrogens.

The study also found a greater protective effect of estradiol and conjugated estrogens for trochanteric hip fractures (relative risk 0.60 (95 percent confidence interval 0.35 to 0.96)) than for cervical hip fractures (0.73 (0.55 to 0.95)) (14). This finding supports earlier claims that trabecular bone, which constitutes a larger part of the bone structure in the trochanteric than in the cervical part of the femur, is more rapidly affected by hormonal changes than is cortical bone.

HRT has also been found to be effective in reducing other types of osteoporosis-related fractures. Cauley and colleagues, reporting on the Study of Osteoporotic Fractures cohort, found a decrease in risk of fractures in elderly women who currently used HRT, but not in elderly women who previously used HRT (l). The Study of Osteoporotic Fractures cohort includes 9,704 nonblack women 65 years of age or older who were recruited from population-based lists from four regions of the United States between September 1986 and October 1988. Members of the cohort were interviewed about HRT use and osteoporosis risk factors upon entry into the study, and women were contacted every four months for up to 6.5 years afterwards to determine whether they had a fracture.

Compared to women who had never used HRT, current users of HRT had a significantly decreased risk for wrist fractures (relative risk 0.46 (95% confidence interval 0.29 to 0.72)) and all nonspinal fractures (relative risk 0.69 (0.57 to 0.83))[1] (l). The relative risk of hip fracture was decreased but not statistically significant (relative risk 0.80 (0.5 1 to 1.26)). By contrast, no association was found between previous use of HRT and the risk for either hip fractures (relative risk 1.00 (0.72 to 1.07)) or for all nonspinal fractures (relative risk 0.97 (0.85 to 1.1 l)). Previous users had a 15-percent decrease in the risk for wrist fracture, but the decrease was not statistically significant (relative risk 0.85 (0.65 to 1.11)). Among current users, the effect of PERT on fracture incidence was similar to the effect of ERT.

The investigators also found that the association between current HRT use and risk for wrist fractures and all nonspinal fractures was similar in those younger and older than 75 years of age (1) (table B-l). They also found an 80 percent decrease in the risk for hip fractures among women older than 75 years of age (relative risk 0.18 (0.04 to 0.77)), but found no effect on hip fracture in those 75 years of age or younger (relative risk 0.94 (0.52 to 1.69)).

Finally, the investigators found that HRT is more effective if initiated within 5 years of menopause and if used longer than 10 years (l). The investigators found little effect of duration of use among current HRT users on the occurrence of all nonspinal fractures, but more than 10 years of use was associated with a substantial reduction in the risk for wrist and hip fractures (table B-l). Women who began using HRT within five years of menopause were found to have substantially greater reductions in risk of wrist, hip, and all nonspinal fractures than women who began using HRT more than 5 years after menopause (table B-l).

[1]The investigators did not examine the incidence of spinal fractures in the cohort.

TABLE B-1: Hormone Replacement Therapy and Fracture (Page

Study	Number of participants	Study design	Type of fracture	Description of study and population	Results[a]
Gordan (1973)	120 on estrogen, 100 on androgens or anabolic steroids	Prospective cohort with internal controls	Fracture type unspecified	Subjects were postmenopausal women, average age 62 at study entry, with osteoporosis as determined by spinal x-ray evidence, who were seen at a San Francisco, CA, clinic between 1948 and 1973. All subjects completed more than two years of hormone therapy. A total of 1,664 patient-years was studied including 1,507 patient-years of CEE and 157 patient-years of androgens and anabolics.	CEE 1.25mg. 3 fractures/1 ,000 patient-years, CEE 0.60mg. 25 fractures/ 1,000 patient-years, Androgens and anabolics 40 fractures/1 ,000 patient-years No tests of statistical significance were provided.
Hammond (1979)	301 estrogen users, 309 controls	Retrospective cohort with Internal controls	Unspecified	Subjects were patients at Duke Hospital or clinics (Durham, NC) between 1940 and 1979 for diagnoses related to estrogen deficiency and who had been followed at Duke for at least 5 years. Estrogen use was defined as use greater than 5 years. Average age at study entry for estrogen users was 42.9 years, whereas average age for nonusers at study entry was 49.6 years. Average age of estrogen users at end of study was 56 years. Only 16 of the estrogen-treated group of 301 patients were black whereas 104 of the 309 patients not treated with estrogens were black.	Estrogen-treated patients had an 8.6% fracture incidence during study period. Patients not treated with estrogen had a 15.9% fracture incidence during study period (relative risk 0.54). No tests of statistical significance were provided.
Hutchinson (1979)	80 cases (107. estrogen users); 80 controls (25% estrogen users)	Hospital-based case-control	Hip and distal radius fractures	Cases were admitted to Yale-New Haven Hospital (Connecticut) between 1974 and 1977. Controls were inpatients from the orthopedic service during those same years, matched for race, age, and discharge date to cases. All cases and controls were between 40 and 80 years of age. Information was gathered through review of medical records and Interviews Estrogen use was defined as use greater than 6 months	Odds ratio “for protection” was 3.0 (p = 0.01) for estrogen users versus nonusers, odds ratio increases to 3.5 if estrogens are begun within 5 years of menopause (p = **0.01**)

TABLE B–1: Hormone Replacement Therapy and Fracture (page 2 of 10)

Study	Number of participants	Study design	Type of fracture	Description of study and population	Results[a]
Lindsay (1 980)	58 mestranol-treated patients; 42 controls	Prospective cohort with internal controls	Spine and radius fractures	Estrogen users and controls were post oophorectomy patients followed at a clinic in Britain for a mean duration of 9 years. Estrogen users were treated with mestranol, 23.3mcg mean dose. All subjects were followed with spinal x-rays. All subjects were elderly patients with preexisting osteoporosis.	There was a significant reduction in wedge deformities of index vertebrae (T4 and L2) estrogen users. No tests of statistical significance were performed.
Weiss (1980)	327 cases (34% estrogen users), 576 controls (52% estrogen users)	Population-based case-control	Hip and distal radius fractures	Cases were white women, aged 50 to 74 years, followed in 59 outpatient orthopedic clinics in King County (Seattle), WA, for hip fractures and wrist fractures that occurred between 1978 and 1979. Controls were of the same ages as cases and selected from the same region. All subjects were interviewed about estrogen use, fracture history, and osteoporosis risk factors.	Current use. relative risk 0.42 (0.30-0.63) in hip fracture patients versus controls. Long-term use (> 10 yr.). relative risk 0.46 (0.30-0,69) in hip fracture patients versus controls. Decreased risk of hip fracture was seen only with more than 5 years of hormonal replacement therapy.
Johnson (1981)	168 cases (29.2% estrogen users); 336 controls (36% estrogen users)	Hospital based case-control	Hip fractures	Cases and controls were members of the Kaiser-Permanente Medical Program of Portland, OR, who were identified through medical records. Cases were women between 52 and 80 years old hospitalized for fracture of the proximal end of the femur between 1965 and 1975. Two hospital controls were selected for each case, matched for age and date of discharge, Estrogen use was ascertained from medical records. Estrogen exposure was defined as written order in the medical records of estrogens taken during or after the year of menopause and prior to hospitalization Authors noted that the number of cases was sufficient only to detect a reduction of risk of about 50 percent or greater.	Relative risk of hip fracture in estrogen users versus nonusers was 0.72 (0.48-1 .09) (p= 0.06). Controls were more likely to have long duration (at least 36 months) of exposure and more likely to begin estrogen within three years of menopause than cases, although differences did not achieve statistical significance.

TABLE B–1: Hormone Replacement Therapy and Fracture (page 3 of 10)

Study	Number of participants	Study design	Type of fracture	Description of study and population	Results[a]
Paganini-Hill (1981)	91 Cases (49% estrogen users); 166 controls (52% estrogen users)	Population-based case-control	Hip fractures	Cases and controls were residents of Leisure World Retirement Community, Los Angeles, CA. Cases were postmenopausal women who had hip fractures between 1974 and 1978, were less than 80 years of age, and were identified from local hospital records. Controls were selected from the retirement community, matched for age, race, and date of entry into the community. Estrogen use was recorded from outpatient medical records and personal interviews.	Relative risk with long-term use (> 60 months) was 0,42 (0.18-0.98) in hip-fracture cases versus community controls. Protective effect of greater than 60 months estrogen use was limited to oophorectomized women, relative risk was 0.14 (0.03-0.70), relative risk of estrogen use in hip fracture cases with natural menopause was 0.86 (nonsignificant).
Kreiger (1982)	98 cases; 884 controls (83 trauma controls, 801 nontrauma control)	Hospital-based case-control	Hip fractures	Cases and controls were admitted to inpatient surgical services at a Connecticut hospital between 1977 and 1979. Controls were admitted for nongynecologic diagnoses. Two control groups were used for comparison: trauma controls and nontrauma controls. Ever use was defined as use greater than 6 months.	Relative risk in ever users versus nonusers was 0.5 (0.3-1.1) for cases and trauma controls, 0.5 (0.3-0.9) for cases and nontrauma controls.
Riggs (1982)	Five groups, including 45 receiving no treatment and 32 receiving estrogen with calcium	Prospective cohort with internal controls	Vertebral fractures	Study subjects were postmenopausal women referred to the Mayo Metabolic Bone Disease Clinic, Rochester, MN, between 1968 and 1980. Estrogen users received 0.625 to 2.5 mg/d of CEE with 1,000 to 3,000 mg/d of calcium. Fifteen estrogen users had also received vitamin D (50,000 units once or twice weekly). Mean age of estrogen users was 63.8, and mean age of untreated group was 62.9. Subjects were followed up in clinic, mean duration of followup for estrogen users was 4,5 years, and for subjects assigned to placebo, 2.0 years.	The fracture rate was 834 per thousand person-years in the untreated patients and 181 per thousand person-years in the estrogen group ($p < 1X10^{-6}$

TABLE B–1: Hormone Replacement Therapy and Fracture (page 4

Study	Number of participants	Study design		Description of study and population	Results[a]
Williams (1982)	344 cases (34% estrogen users); 567 controls (52% estrogen users)	Population-based case-control	Hip and forearm fractures	Study subjects were white women ages 50 to 74 who had sustained hip or forearm fractures between 1976 and 1979. Cases were followed by orthopedic surgeons in King County, Washington. Controls were a random sample of white female residents of King County in the same age range. Estrogen use was ascertained by interviews with study subjects.	The beneficial effect of estrogen use in preventing hip and forearm fractures varied according to a woman's weight and smoking status, being greatest in thin women who smoked cigarettes and near zero in heavy nonsmokers. Reduction in risk of forearm fracture in thin smokers by use of estrogen. 4.7 Reduction in risk of hip fracture in thin smokers by use of estrogen: 7.1 Reduction in risk of forearm fracture in average weight smokers by use of estrogen: 0.8 Reduction in risk of hip fracture in average weight smokers by use of estrogen. 4,4 No tests of statistical significance were done.

TABLE B–1: Hormone Replacement Therapy and Fracture (page 5 of 10)

Study	Number of participants	Study design	Type of fracture	Description of study and population	Results[a]
Ettinger (1985)	245 estrogen users; 245 controls	Retrospective cohort with internal controls	Wrist, spine, and all fractures	Study subjects were white postmenopausal women, average age 73 years, identified from review of pharmacy records dated between 1968 and 1971. Black women were excluded from the study because of the low incidence of fractures in this group. Subjects were followed for an average of 17.6 years. Study subjects were followed at the Kaiser Permanence Medical Center, San Francisco, CA. Controls were matched for age and length of membership in the health plan, Estrogen use was defined as use begun within three years of menopause and at least 5 years of estrogen use. Fracture incidence and continued estrogen use was determined by reviewing medical records.	Relative risk for osteoporotic fracture was 2.2 (1 ,5-3.8) (in nonusers versus users); relative risk for spine fracures was 2.7 (1 .0-8.1). There was no significant difference in risk of hip fractures or wrist fractures between users and nonusers,
Kiel (1987)	2,873 women (667 estrogen users)	Retrospective cohort with internal controls	Proximal femur fractures	Study subjects were members of the Framingham (Massachusetts) Heart Study cohort between 1948 and 1985. Subjects were ages 30 to 62 years old at the 1st biennial examination held between 1948 to 1951. Only women who reached menopause during the study interval were included in this analysis. Information on fractures was gathered from review of hospital records and interviews of subjects at the cohort's 18th biennial examination (1983-1985). Subjects had provided information about estrogen use at most of the biennial examinations.	Unadjusted relative risk in women who have taken estrogen within the previous two years versus never users was 0,34 (0.08-0,64), Unadjusted relative risk in women with any estrogen use versus nonusers was 0.69 (0.46-1 .03). Unadjusted relative risk for recent users of less than one year was 0.32 (0.09-1 .21); relative risk in recent users for more than one year was 0.14 (0.03-0.76).

TABLE B–1: Hormone Replacement Therapy and Fracture (page 6 of 10)

Study	Number of participants	Study design	Type of fracture	Description of study and population	Results[a]
Naessn (1 990)	23,246 women (all HRT users)	Prospective cohort with external controls	Hip fractures	Cohort included all women 35 years of age or older from the Uppsala Health Care Region of Sweden who received noncontraceptive estrogens from April 1977 to March 1980. Comparisons were made with expected rates of incidence of hip fracture in women in the background population. Women were followed for an average of 5.7 years.	Relative risk was 0.79 (0.68 to 0.93) in estrogen users compared with the background population
Paganini-Hill (1991)	8,600 women (4,866 ever estrogen users)	Prospective cohort with internal controls	Hip fractures	Cohort Includes postmenopausal women who were residents of Leisure World Retirement Community, Los Angeles, CA. Mean age of residents was 73 years. Mailed questionnaires were sent in 1981, 1982, 1983, and 1985. Cohort was followed for area hospital admissions and local health department death certificates through 1988.	Relative risk for ever use was 1.02 (0.81-1 .27) Dose, < 0.625mg CEE: 0.84 (0.58-1 .21) > 1,25mg CEE: 0.91 (0.64-1.29) Duration: <3 years, 1,19 (0.89-1 .60) 4-14 years: 0,89 (0.63-1 .23) >15 years 0,88 (0,63-1 .24) Recency (years since last estrogen use): >15 years: 1,15 (0.88-1 .50) 2-14 years. 0.88 (0.63-1 .23) O-1 years. 0.80 (0.53-1 .21) Duration and Recency. <3 years, >15 yrs. 1,33 (0.97-1 ,82) 2-14 yrs. 0.79 (0.38-1 .60) O-1 yrs. 0.87 (0.28-2.73) 4-14 years: > 15 yrs. 0.95 (0.61 -1.49) 2-14 yrs. 0.86 (0.52-1 .42) O-1 yrs. 0.72 (0.31-1 ,64) > 15 years: > 15 yrs. 0.57 (0.1 8-1 .79) 2-14 yrs. 0,97 (0.61-1 .53) O-1 yrs. 0.85 (0.53-1 .38)

TABLE B–1: Hormone Replacement Therapy and Fracture (page 7 of 10)

Study	Number of participants	Study design	Type of fracture	Description of study and population	Results[a]
Kanis (1992)	2,086 cases, 3,532 controls	Population-based case-control	Hip (femoral neck) fractures	The Mediterranean Osteoporosis Study examined the incidence of hip fracture in men and women aged 50 years or over from 14 centers from six countries in Southern Europe. Cases were women over age 50 (mean age 78 years) who had a hip fracture over a one-year period (1988 to 1989). Cases were identified by surveillance of hospitals, private clinics, and nursing homes in the catchment area. Controls of the same age and who were neighbors of cases or were sampled from population registers were identified. Information about use of drugs affecting bone was obtained by interview. Investigators from each center provided prospective information. Only 1.9 percent of cases and 3.5 percent of controls had ever used estrogen.	Relative risk 0.45 (0,30 to 0,67) (P = 0.0001) in ever users versus never users. Adjusted relative risk 0,55 (0,36 to 0.85) (p = 0.01) (adjusted for center, age, body mass index, and previous fragility fractures). Fracture risk stratified by age, <80 years, Adjusted relative risk 0.51 (0.31 to 0.84) (p = 0.009) >80 years, Adjusted relative risk 0,70 (0.29 to 1.66) (NS) Duration: Less than median duration of estrogen use: relative risk 0.86 (0.51 to 1,46) Greater than median duration: relative risk 0.29 (0.1 3 to 0,61)
Lufkin (1992)	75 women	Randomized clinical trial	Vertebral fractures	Study subjects were postmenopausal white women, 47 to 75 years of age, with established osteoporosis (defined as BMD below the 1Oth percentile of normal postmenopausal women and one or more vertebral fractures) seen at Mayo Clinic, Rochester, MN. Subjects were randomly assigned to placebo or treatment with transdermal estrogen (Estraderm patch) for 3 weeks out of a 4-week cycle, with 10 mg/d oral medroxyprogesterone acetate. The study duration was one year.	Eight new fractures occurred to seven women in the estrogen group, whereas 20 new fractures occurred in 12 women in the placebo group (relative risk 0.39 (0.16 to 0.95).

TABLE B–1: Hormone Replacement Therapy and Fracture (page 8 of 10)

Study	Number of participants	Study design	Type of fracture	Description of study and population	Results[a]
Spector (1992)	1,075 HRT users, 1,471 controls	Retrospective cohort with external controls	Osteoporotic fractures	HRT users were women, average age 52, who attended a Dulwich, South London, UK, menopause clinic for hormone replacement therapy between January 1976 and December 1986. Controls were postmenopausal women of the same age from the registers of four general practices in Greater London. Information was gathered by questionnaire and review of medical records. Most HRT users (65%) received subcutaneous estrogen implants (50 to 100 mg estradiol) every six months, usually in combination with 100 mg testosterone. Cyclical progestins were given for 12 days each cycle to most estrogen users who had not had a hysterectomy. Average duration of HRT use was 51 months.	Relative risk of distal radius fractures was 0.70 (0.32 to 1,55) compared with pre-HRT fracture rates and 0.63 (0.31 - 1.31) compared with nonusers. Relative risk of osteoporotic fractures was 0.96 (0.55 - 1.68) compared with pre-HRT fracture rates and 0.71 (0.43 to 1.16) compared with nonusers. There was a trend toward decreased incidence of fractures with increased duration of use for osteoporotic fractures (P = 0.06) and wrist fractures (p= ***0.03).*** There were 6 reported fractures of the hip in the nonusers compared with none among estrogen users (p = 0.15).
Grisso (1994)	144 cases (4% HRT users), 218 community controls (8% HRT users), 181 hospitalized controls	Case-control study with both hospital and community controls	Hip fracture	Cases were black women admitted with first hip fracture to 1 of 30 hospitals in New York and Philadelphia, Community controls were black women living in the community who were matched to cases by age and geographic area, Hospital controls were black women matched by age and hospital. Information was obtained through personal interviews.	Fracture risk stratified by age*: Less than 75 years old: adjusted odds ratio 0.05 (0.01 -0.6) compared with community controls adjusted odds ratio 0.1 (<0.1 -0.5) compared with hospital controls

TABLE B–1: Hormone Replacement Therapy and Fracture (page 9 of 10)

Study	Number of participants	Study design	Type of fracture	Description of study and population	Results[a]
Grisso-cent. (1994)					Age 75 years or more: adjusted odds ratio 0.3 (0.1 -1 .2) compared with community controls adjusted odds ratio 1.1 (0.2-6.3) compared with hospital controls Duration*: 1 to 6 years: adjusted odds ratio 0.7 (0.2-3.1) more than 7 years: adjusted odds ratio 0.2 (0.1-1 .0) compared with community controls Recency (time since last use)*: less than 5 years: adjusted odds ratio 0.0 (0-0.95) 5 or more years: adjusted odds ratio 0.6 (0,2-1 .7) compared with community controls •All results are for HRT use for 1 year or more
Lafferty (1994)	157 women (52% estrogen users)	Prospective cohort with internal controls	Vertebral compression fractures and peripheral fractures	Study subjects were all white postmenopausal women between 43 and 60 years of age seen in a Cleveland, OH, private practice between 1964 and 1983. Subjects were followed though 1989, All estrogen users received 0.625mg/day CEE for the first 25 days per month After 1983, 5mg/day of medroxyprogesterone acetate was given for 12 days each month, Estrogen use was defined as use of at least 3 years duration (68% of ERT users took estrogens for more than 10 years).	Relative risk of spinal compression fracture 0.27 (0.12-0.60) in estrogen users versus nonusers; relative risk of peripheral fracture was 0.23 (0.06-0.97); relative risk of all fractures was 0.28 (0.09-0.89).

TABLE B–1: Hormone Replacement Therapy and Fracture (page

Study	Number of participants	Study design	Type of fracture	Description of study and population	Results[a]
Cauley (1995)	9,704 women (13.7% current users) (27.4°A ever users)	Prospective cohort with internal controls	Hip fractures, wrist fractures, and all nonspinal fractures	Subjects were nonblack women 65 years of age or older who were members of the Study of Osteoporotic Fractures cohort, a prospective study conducted at four clinical centers in the United States. The SOF cohort was recruited from population-based lists of women (voter registration, driver's license, and health maintenance organization membership lists). Black women were excluded because of their low incidence of fractures. Information on HRT use and risk factors was gathered from interviews at baseline and information about incident fractures was gathered by postcard or telephone every 4 months. Subjects were recruited from September 1986 to October 1988, and followed through March 1993. Duration of followup ranged from 0.02 to 6.5 years.	Current versus past HRT use: Hip fractures: current HRT use: age adjusted relative risk 0.80 (0.51-1 .26) risk-factor adjusted relative risk' 0.60 (0,36-1 .02 past HRT use: age adjusted relative risk 1.00 (0.72-1 .07) risk-factor adjusted relative risk 1.03 (0.69-1 .55) Wrist fractures: current HRT use: age adjusted relative risk 0.46 (0.29-0.72) risk-factor adjusted relative risk 0.39 (0.24-0.64) past HRT use: age adjusted relative risk 0.85 (0.65-1 .11) risk-factor adjusted relative risk 0.81 (0,62-1 .07) All nonspinal fractures, current HRT use: age adjusted relative risk 0.69 (0.57-0.83) risk-factor adjusted relative risk 0.66 (0.54-0.80) past HRT use. age adjusted relative risk 0.97 (0.85-1 .11) risk-factor adjusted relative risk 0,94 (0,83-1 .08)

* Relative risk was adjusted for multiple osteoporosis risk factors

[a]95 percent confidence intervals are given in parentheses, unless otherwise specified

KEY: BMD = bone mineral density; CEE = conjugated equine estrogen, ERT = estrogen replacement therapy; HRT = hormonal replacement therapy;

SOURCE: Office of Technology Assessment, 1995

Providing further support for the proposition that hormonal replacement therapy reduces fracture incidence are a number of clinical trials of hormonal replacement therapy in postmenopausal women which demonstrate statistically significant reductions in incidence of osteoporosis-related fractures other than hip fracture in users of hormonal replacement therapy (13,17) (table B-l).

One controlled clinical trial demonstrated the effectiveness of hormonal replacement therapy in reducing the incidence of vertebral fractures in a group of women with established osteoporosis (13). In this study, 75 postmenopausal women, 47 to 75 years of age, with one or more vertebral fractures due to osteoporosis, were randomly assigned to treatment with an estradiol patch and oral medroxyprogesterone acetate or a placebo patch. Bone mineral density and vertebral fractures were assessed at the beginning of the study and after one year. Bone mineral density was maintained or increased in the treatment group at all sites measured. Eight new fractures occurred in 7 women in the estrogen group, whereas 20 occurred in 12 women in the placebo group, yielding a significantly lower vertebral fracture rate in the estrogen group (relative risk 0.39 (95 percent confidence interval 0.16 to 0.95)).

Estrogen treatment would probably also decrease hip fracture rates, as it does vertebral fracture rates, because bone mineral density in the estrogen group increased at the hip sites studied. The reduction in hip fracture rates may not be proportional to the reduction in vertebral fracture rates, however, in part because of differences in the qualitative features of the bone at both sites, and because such factors as neuromuscular weakness, postural instability, and the tendency to fall play a greater role in fractures of the hip.

Controlled clinical trials of the relation between HRT use and vertebral fracture have been possible because of the relatively large number of vertebral fractures in postmenopausal women and the relatively early age at which vertebral fractures typically occur. Conducting a controlled clinical trial of hormonal replacement therapy and hip fracture presents much greater problems, however, due to the relatively low incidence of hip fractures relative to vertebral fractures, the long duration between menopause and the age at which most hip fractures occur (above 65 years), and difficulties in maintaining compliance with hormonal replacement therapy over that long a time period.

REFERENCES

1. Cauley, J., Seeley, D., Ensrud, K., et al., "Estrogen Replacement Therapy and Fractures in Older Women," *Annals of Internal Medicine* 122:9-16, *1995.*
2. Ettinger, B., Genant, H. K., and Cann, C. E., "Long-Term Estrogen Replacement Therapy Prevents Bone Loss and Fractures," *Annals of Internal Medicine* 102(3):319-324, *1985.*
3. Gordan, G., Picchi, J., and Roof, B., "Antifracture Efficacy of Long-Term Estrogens for Osteoporosis," *Transactions of the Association of American Physicians* 86:326-332, 1973.
4. Grisso, J., Kelsey, J., Strom, B., et al., "Risk Factors for Hip Fracture in Black Women," New *England Journal of Medicine 330(22): 1555-1559, 1994.*
5. Hammond, C., Jelovsek, F., Lee, L., et al., "Effects of Long-Term Estrogen Replacement Therapy: I. Metabolic Effects," *American Journal of Obstetrics and Gynecology* 133(5):525-536, *1979.*
6. Hutchinson, T., Polansky, S., and Feinstein, A., "Postmenopausal Oestrogens Protect Against Fractures of Hip and Distal Radius: A Case Control Study," *Lance? 705-709, 1979.*
7. Johnson, R. E., and Specht, E. E., "The Risk of Hip Fracture in Postmenopausal Females with and Without Estrogen Drug Exposure," *American Journal of Public Health* 71(2); *138-144, 1981.*
8. Kanis, J. A., Johnell, O., Gullberg, B., et al., "Evidence for Efficacy of Drugs Affecting Bone Metabolism in Preventing Hip Fracture," *British Medical Journal* 305(7): *1124-1128, 1992.*

9 Kiel, D.P., Felson, D.T., Anderson, J. J., et al., "Hip Fracture and the Use of Estrogens in Postmenopausal Women: The Framingham Study," New *England Journal of Medicine* 317(19):1169-1174, *1987.*

10 Kreiger, N., Kelsey, J.L., Holford, T.R., et al., "An Epidemiologic Study of Hip Fracture in Postmenopausal Women," *American Journal of Epidemiology* 116(1): 141-148, 1982.

11. Lafferty, F.W., and Fiske, M. E., "Postmenopausal Estrogen Replacement: A Long-Term Cohort Study," *American Journal of Medicine* 97(1):66-77, 1994.

12. Lindsay, R., Hart, D. M., Forrest, C., et al., "Prevention of Spinal Osteoporosis in Oophorectomized Women," *Lancet* 1151-1154, 1980.

13. Lufkin, E.G., Wahner, H. W., O 'Fallen, W.M., et al., "Treatment of Postmenopausal Osteoporosis with Transdermal Estrogen," *Annals of Internal Medicine 117(1):1-9, 1992.*

14. Naessen, T., Persson, I., Adami, H. O., et al., "Hormone Replacement Therapy and the Risk for First Hip Fracture," *Annals of Internal Medicine* 113:95-103, *1990.*

15. Paganini-Hill, A., Chao, A., Ross, R. K., et al., "Exercise and Other Factors in the Prevention of Hip Fracture: The Leisure World Study," *Epidemiology 2(l): 16-25, 1991.*

16. Paganini-Hill, A., Ross, R. K., Gerkins, V.R., et al., "Menopausal Estrogen Therapy and Hip Fractures," *Annals of Internal Medicine* 95(1):28-31, *1981.*

17. Riggs, B. L., Seeman, E., Hodgson, S.F., et al., "Effect of the Fluoride/Calcium Regimen on Vertebral Fracture Occurrence in Postmenopausal Osteoporosis," New *England Journal of Medicine* 306(8):446-450, *1982.*

18. Spector, T. D., Brennan, P., Harris, P. A., et al., "Do Current Regimes of Hormone Replacement Therapy Protect Against Subsequent Fractures?" *Osteoporosis International* 2:219-224, *1992.*

19. Weiss, N. S., Ure, C. L., Williams, J. H., et al., "Decreased Risk of Fractures of the Hip and Lower Forearm with Postmenopausal Use of Estrogen," New *England Journal of Medicine* 303(21):1195-1198, *1980.*

20. Williams, A.R., Weiss, N. S., Ure, C. L., et al., "Effect of Weight, Smoking, Estrogen Use on the Risk of Hip and Forearm Fractures in Postmenopausal Women," *Obstetrics & Gynecology* 60(6):695-699, *1982.*