Effectiveness and Costs of Osteoporosis Screening and Hormone Replacement Therapy, Vol. II: Evidence on Benefits, Risks, and Costs

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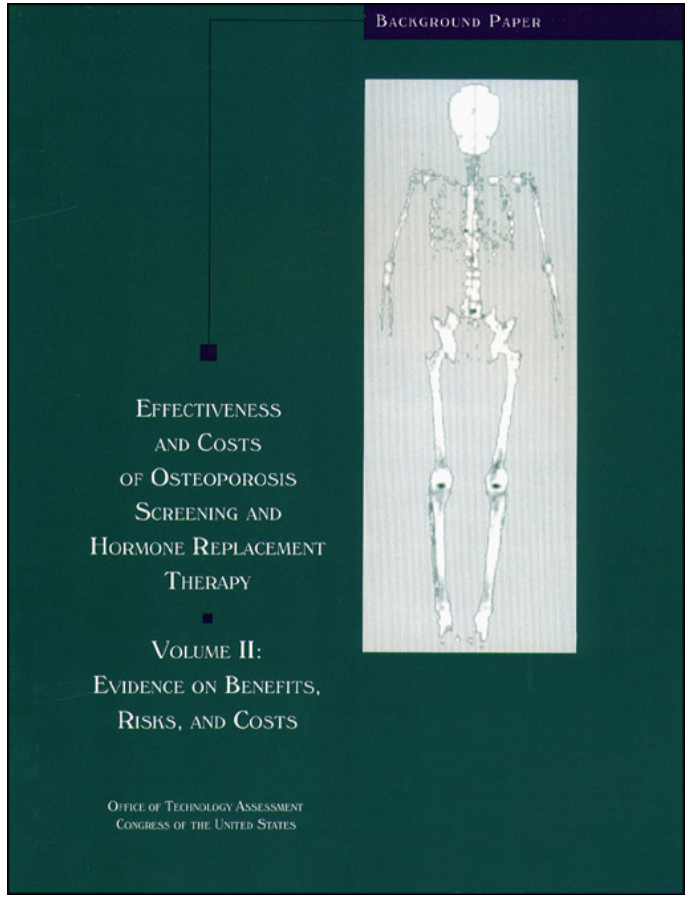

Foreword

Menopause typically occurs in women around age 50. Accompanying this life event is a decline in estrogen levels and an increase in the rate of decline in women's bone density. This rapid bone loss increases women's subsequent risk of developing osteoporosis, a disease characterized by low bone density and increased bone fragility. Among the most serious consequences of osteoporosis is fracture of the hip, which may result in substantial morbidity, prolonged hospitalization, and death. Estrogen can prevent bone loss after menopause by replacing the body's own estrogen. Given the serious consequences of osteoporosis, some osteoporosis experts have recommended that women have their bone mineral density measured at the time of menopause and those with the lowest bone mineral density be offered *hormone replacement therapy,* comprising estrogen given alone or in combination with the hormone progestin.

This background paper, *Effectiveness and Costs of Osteoporosis Screening and Hormone Replacement Therapy,* assesses the medical benefits and costs of both screening and hormone replacement therapy. It is divided into two volumes. The first volume, *Cost-Effectiveness Analysis,* presents the results of a model that estimates the cost per year of life gained from osteoporosis screening and hormone replacement therapy in postmenopausal women. The second volume, *Evidence on Benefits, Risks, and Costs,* provides the basis for the assumptions about the costs and effects of screening and hormonal replacement therapy used in the cost-effectiveness model.

This background paper is one of three documents resulting from OTA's assessment of policy issues in the prevention and treatment of osteoporosis. This assessment was requested by the Senate Special Committee on Aging, Senator Charles Grassley and Senator John Glenn, and the House Select Committee on Aging, Representative Olympia J. Snowe, Representative Benjamin A. Gilman, and former Representatives Brian J. Donnelly, Thomas J. Downey, and Patricia F. Saiki. Two background papers in this series have been issued, both in July 1994: *Public Information about Osteoporosis: What's' Available, What's Needed?,* and *Hip Fracture Outcomes in People Age Fifty and Over.*

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Preface

This volume, "Evidence on Benefits, Risks, and Costs of Hormonal Replacement Therapy," is a companion to the volume "Cost-Effectiveness Analysis" of the OTA background paper "Effectiveness and Costs of Osteoporosis Screening and Hormone Replacement Therapy." This volume reviews evidence on the impact of hormonal replacement therapy (HRT) on bone density, fractures, breast cancer, endometrial cancer, gallbladder disease, and heart disease that underlies the assumptions used in OTA's cost-effectiveness analysis. This volume also includes information about hormonal replacement therapy dosage regimens; reviews the relationship between bone mineral density and hip fracture; and summarizes the costs of bone mineral density screening, intervention, and diseases affected by HRT.

This volume is organized as a series of appendices. Several appendices review HRT's impacts on disease, including:

- Appendix B: "Evidence on Hormonal Replacement Therapy and Fractures,"
- Appendix F: "Evidence on Hormonal Replacement Therapy and Breast Cancer,"
- Appendix G: "Evidence on HRT and Endometrial Cancer, "
- Appendix H: "Evidence on HRT and Gallbladder Disease," and
- Appendix I: "Evidence on HRT and Coronary Heart Disease."

Appendix D, "Summary of Hip Fracture Prediction Methods," details the method for predicting the number of hip fractures used in OTA's cost-effectiveness analysis. The appendix describes the specific parameter assumptions and sources of data regarding the longitudinal distribution of bone mass in menopausal women from ages 50 to 90. The appendix also describes the specific parameter assumptions and sources of data regarding the short-term relationship of bone mass to fractures at each age.

Appendix E, "Hormonal Replacement Therapy Regimens," describes the types of estrogens and progestins used for hormonal replacement therapy, their doses, and their administration. The appendix also describes the impact of hormonal replacement therapy on menopausal symptoms, and adverse effects of HRT, such as bleeding and premenstrual-tension-like symptoms. The appendix also describes the impact of these various dosage regimens on compliance with HRT.

Appendix J, "Methods for Estimating Costs," provides the basis for OTA's assumptions concerning the costs of bone mineral density measurement, hormone replacement therapy, heart disease, hip fractures, gallbladder disease, endometrial cancer, and breast cancer.

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Appendix A: Acknowledgments

A

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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.

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Appendix C: Evidence on HRT and Bone Loss

C

A large number of controlled clinical trials have demonstrated that hormone replacement therapy (HRT) is able to reduce the rate of bone loss in postmenopausal women. Most of the controlled clinical trials of HRT on bone mass have been for a duration of three or fewer years (table C- 1). The first pages of table C-1 ("HRT and Bone Mineral Density: Clinical Trials of 3 or Fewer Years") provide details of the design and results of each of the studies. The percentage change in bone mass from the baseline measurement to the end of the study is provided so that we may compare bone mass data that are given in disparate units (e.g., bone mineral content (usually measured in grams per centimeter (g/cm)) and bone mineral density (usually measured in grams per square centimeter (g/cm^2)).

Virtually all of these studies have shown that HRT, begun soon after menopause, maintains or increases bone mass within the first three years after menopause. Although HRT may reduce the rate of bone loss after menopause, HRT is not able to substantially restore bone mass that is lost. The increases in bone mass seen with initiation of therapy soon after menopause are small, generally in the range of 1 to 3 percent of the total bone mass.

A number of investigators have questioned whether there is a significant subgroup of postmenopausal women who fail to respond to HRT (16). Recent analyses have found that the proportion of women who fail to respond to hormone replacement therapy is relatively small (20).

Only a handful of studies of HRT and bone mineral density have followed women more than three years after initiation of therapy (table C-2), and these studies have shown that HRT maintains bone mass or reduces the rate of bone loss in postmenopausal women compared with placebo. In a retrospective cohort study, Meema and colleagues contacted postmenopausal women who had a bone mass measurement at a university clinic four to 10 years previously and asked them to volunteer for a second bone mass measurement (36). Eighty two volunteers were identified, 29 of whom had been treated continuously with estrogens. After an average followup period of six years, the estrogen-treated women showed no significant changes in bone mass and cortical thickness, whereas untreated women had significant decreases in bone mass and cortical thickness. In a cross-sectional study, Moore examined the bone mineral density of 65 postmenopausal women between 55 and 75 years of age who were at least 10 years from menopause (37). Long-term estrogen users were defined as those women who had begun therapy within five years of menopause and

TABLE C-1: HRT and Bone Mineral Density: Selected Clinical Trials of 3 or Fewer Years (Page 1 of 7)

Study	Number of part' 'p	Duration of monitoring of bone	Type of	Results	
Aitke (' 973)	68 treated; 56 controls	1 years	Ten treated patients and 10 controls two months post-oophorectomy; 41 treated patents and 39 controls three years post-oophorectomy; and 17 treated patients and 17 controls six years post oophorectomy. Treated patients received mestranol in an average daily dose of 20 mcg.	Placebo: ▪ Two months post-oophorectomy ▪ Three years post-oophorectomy ▪ Six years post-oophorect Mestranol-treated patients: ▪ Two months post-oophorectomy ▪ Three years post-oophorectomy ▪ Six years post-oophorectomy	 -3.9 % -0.3 % -0.9 % -0.1 % 2.4 % -0.9 %
Recker 19/7)	18 treated; 20 controls; 22 Ca CO_3 2,600mg	2 years	Patients divided into three groups: Group I received placebo; Group II received conjugated equine estrogen, 0.625mg, and methyl testosterone, 5mg, 21 days of each month; Group III received 2,600mg calcium carbonate daily	Control Hormone-treated Calcium-carbonate treated	-5.75% -1.32% -3.65%
Lindsay (' 978a)	10 mestranol; 10 gestranol; 10 placebo	1 year	Patients randomized to three groups; Group I: mestranol 40mg/day; Group II: gestranol hexanoate (Depostat) 200mg IM every month for 3 months, then every 3 months; Group III: placebo	Mestranol Gestranol Placebo	+1.33% +0.22% -3.76%
Christiansen 1980)	2' Trisequens orte; 103 placebo	2	315 women randomized to seven treatment groups and placebo group: all patients received 500mg calcium daily; hormone replacement therapy group (21 patients) received Trisequens forte; 264 patients completed study	Placebo HRT	-3.3 % +2.5 %
Christiansen (1981a)	23 placebo; 21 1,25$(OH)_2$ D_3 ; 21 1,25$(OH)_2$ D_3 + hormones; 19 hormones	1 year	One control group and three treatment groups: 1,25$(OH)_2$ D_3 (0.25mg/d); Trisequens forte; 1,25$(OH)_2$ D_3 (0.25mg/d) + Trisequens forte; placebo control Trisequens: estradiol, estriol, and norethisterone acetate	1,25$(OH)_2$ D_3 Placebo 1,25$(OH)_2$ D_3 + hormones Hormones	-2.1±0.5% -2.0±0.5% +0.5±0.5% +1.5±0.5%

TABLE C-1: HRT and Bone Mineral Density: Selected Clinical Trials of 3 or Fewer Years (Page 2 of 7)

Study	Number of participants	Duration of monitoring of bone density	Type of treatment	Results	
Christiansen (1981 b)	part I: 43 treated; 51 controls. Part II: 35 treated, 42 controls	3 years, Part I: first two years of study; Part II: third year of study	Patients treated with Trisequens forte (17-beta-estradiol (4mg) and estriol (2mg) days 1-12, 17-beta-estradiol (4mg) estriol (2mg) and norethisterone acetate 1 mg days 13-22, 17-beta-estradiol (1 mg) and estriol (0.5mg) days 23-28), All patients received 500mg calcium per day.	Part I: HRT (g/cm) Placebo Part II: HRT Placebo HRT Placebo	 2.5% -3.8% 3.7% *0.2%* *-2.4%* -5.7%
Finn Jensen (1 982)	31 treated; 43 controls	18 mo. (6 mo. run-in period)	Patients divided into four groups, 1,25$(OH)_2D_3$(0.50 mg/d) + 500mg calcium, 19 patients; Trisequens + 500mg calcium, 11 patients; 1 ,25$(OH)_2D_3$(0.50mg/d) + Trisequens + 500mg calcium: 20 patients; 500mg calcium 24 patients	Post six month run-in period, 1,25 + calcium calcium + hormones 1,25 + hormones + calcium calcium	 *-1.91 %* *+3.62%* *+3.06%* *-0.39%*
Lindsay (1984)	887 treated patients divided among four groups; 21 controls	2 years	Patients assigned to either placebo group or to CEE at one of four dosage levels: 0,15mg/day, 0.3mg/day, 0.625 mg/day, and 1.25mg/day	Placebo 0.15mg/d 0.30mg/d 0.625mg/d 1.25mg/d	-8.23% -8.51 % -5.01 % -0.24% -0.00%
Christiansen (1984)	2 treatment groups and one placebo group, E_2+E_3 +P: 22 patients; E_2+P: 20 patients; placebo group: 23 patients	1 year	Two treatment groups, 17 beta-estradiol and norethisterone acetate; 17 beta-estradiol, estriol, and norethisterone acetate, placebo group Daily doses used were, 17-beta-estradiol 2mg from days 1-22, 1 mg from days 23-28, estriol: 1 mg days 1-22, 0.5mg days 23-28, norethisterone acetate, 1 mg days 13-22. All patients received 500mg/d calcium,	E_2+P E_2+E_3+P Placebo	+0.52% +1.53% -3.3%

TABLE C-1: HRT and Bone Mineral Density: Selected Clinical Trials of 3 or Fewer Years (Page 3 of 7)

Study	Number of participants	Duration of monitoring of bone density	Type of treatment	Results	
Caniggia (1984)	22 patients group 1: (n=5) 1,25$(OH)_2D_3$, group 2: (n=5) estradiol valerate, group 3: (n=7) 1,25$(OH)_2$ D & estradiol valerate group 4: (n=5) placebo	1 year	Four groups: l ,25 $(OH)_2D_3$ (0.5mcg) ■ ,25 $(OH)_2D_3$ 0.5mcg+ estradiol valerate (2mg/d) ■ stradiol valerate (2mg/d) n placebo No statistical analysis of data.	Placebo 1 ,25$(OH)_2D_3$ 1 ,25$(OH)_2D_3$+-E_2 E_2	-8.O% +9.O% +6.0% +9.0%
Gotfredsen (1986)	52 treated, 52 controls	1 year	Treated patients received either 17-beta-estradiol, either percutaneously (one daily dose of 5g, corresponding to 3mg 17-beta-estradiol) or orally (sequentially administered oral 17-beta-estradiol 2mg and for 10 days each cycle 1 mg cyproterone acetate).	Placebo: Head Chest Arms Pelvis Legs Spine HRT: Head Chest Arms Pelvis Legs Spine DPA lumbar spine. HRT Placebo DPA total spine. HRT Placebo SPA forearm HRT Placebo	 -5. O+-1.5% -7.0+-2.0% -3.0+-1.0% -5.5+-1.5% -4.3+-0.3% -3.0+-2.5% + *1 . 7 + - 1 . 3 %* +2.3+-2.0% +0.3+-0.5% -1.0+-2.0% -0.7+-0.25% -2.1+-1.5% + 1.0% 0.0% 0.0% -2.5% o o% -2.0%

TABLE C-1: HRT and Bone Mineral Density: Selected Clinical Trials of 3 or Fewer Years (Page 4 of 7)

Study	Number of participants	Duration of monitoring of bone density	Type of treatment	Results	
Riis (1987a)	1 placebo controls; 14 calcium; 11 estrogen	2 years	Patients randomly allocated to three groups; percutaneous 17 beta-estradiol 3mg/d for 24 days each 28 day cycle; calcium carbonate 2,000mg per day; placebo. Code was partly broken after one year of treatment and estrogen group received cyclic supplementation of progesterone 200mg from days 13 through 24.	Proximal forearm: Estrogen Calcium Placebo Total body (g): Estrogen Calcium Placebo Distal forearm: Estrogen Calcium Placebo Spine: Estrogen Calcium Placebo	 +0.0% -4.0% -6.0% -0.5% -5.5% -8.0% -1.0% -6.0% -8.2% +3.8% -3.0% -1.8%
Riis (1987b)	29 treated; 28 placebo	2 years	Patients received either 3mg percutaneous estradiol or placebo; code was broken after one year of treatment, and women receiving estradiol continued with a cyclic addition of progesterone, whereas those with placebo continued to receive placebo.	Proximal HRT Placebo Distal HRT Placebo Spine HRT Placebo	 -0.5% -6.0% 0.0% -7.5% +5.5% -2.3%
Civitelli 1988)	11 conjugated estrogens; 10 placebo	1 year	Patient treated with CEE 1.25mg/day; all patients daily intake was maintained in the range of 800-1,000mg of calcium	Femoral shaft Placebo CEE vertebral bodies Placebo CEE	-2.22% +8.3% -2.89% +9.12%

TABLE C-1: HRT and Bone Mineral Density: Selected Clinical Trials of 3 or Fewer Years (Page 5 of 7)

Study	Number of participants	Duration of monitoring of bone density	Type of treatment	Results	
Munk-Jensen (1988)	50 continuous estrogen and progestogen; 50 sequential estrogen and progestogen, 51 placebo	18 months (including 6 mo. run-in period)	Group 1, continuous estradiol 2mg and norethisterone acetate 1 mg; group 2, cyclic estradiol 2mg and 10 days per month 1 mg norethisterone acetate; group 3, placebo. 6 month run-in period where all patients were untreated	Distal forearm, Estrogen and progesterone (continuous) Estrogen and progesterone (sequential) Placebo Lumbar spine: Estrogen and progesterone (continuous) Estrogen and progesterone (sequential) Placebo	 -0.8+-0.6% -2.0+-O.5% -5.6+-0.55% **+4,2+-.8%** +3.2+-0.55% -2.6±0.45%
Riis (1988)	21 treated, 22 controls	2 years	Patients assigned to either continuous 17-β-estradiol, 2mg, and norethisterone acetate, 1 mg, or placebo	Forearm (prox,). HRT Placebo Forearm (distal): HRT Placebo Spine: HRT Placebo	 **+1.0+-1.9%** **-4.5+-2.7%** **+0.8+-3.8%** **-7.5+-3.8%** +5.4+-7.7% -3.7+-8.0%
Genant (1 990)	94 treated; 28 placebo-controls	1 year	30 patients treated with 0.3mg estrone sulfate; 32 patients treated with 0.65mg estrone sulfate, 32 patients treated with 1.25mg estrone sulfate. Purpose of study was to determine minimum effective dose of estrogens. All patients given 1,000mg elemental calcium supplementation	0.3mg estrone sulfate 0.625mg estrone sulfate 1.250mg estrone sulfate Placebo	-3.22% +1.38% +2.62% -0.82%
Lindsay (1990)	22 estrogen treated; 18 controls	2 years	All treated and controls given calcium to bring their total intake to 1,500mg/d, treated patients received CEE 0.625 mg/d, and those with an intact uterus received medroxyprogesterone 5 to 10mg for 12-14 days a month	Vertebrae. Controls Treated Hip: Controls Treated	 -7.6% +6.4% -4.13% +9.2%

TABLE C-1: HRT and Bone Mineral Density: Selected Clinical Trials of 3 or Fewer Years (Page 6 of 7)

Study	Number of participants	Duration of monitoring of bone density	Type of treatment	Results	
Resch (1990)	9 treated, 9 controls	1 year	Nine patients treated with Trlsequens; nine patients treated with placebo, all patients received 500mg calcium; Trisequens is estradiol (2mg) and norethisterone acetate (1 mg)	HRT Placebo	+8.84% 0.0%
Stevenson (1990)	66 treated, 30 controls	18 mos.	33 patients treated with transdermal 17β estradiol 0.05mg daily with transdermal norethisterone acetate 0.2mg to 0.3mg per day for 14 days a cycle; 33 patients treated with oral CEE 0.625mg daily with dl-norgestrel 0.15mg daily for 12 of the 28 days	Transdermal: Spine (L2-L4) Femoral neck Wards triangle Trochanteric Oral HRT: Spine Femoral neck Wards triangle Trochariteric Untreated: Spine Femoral neck Wards triangle Trochanteric	 +3. 14% +3. 14% +1.0% 0.0% +1.71% +1.00% +2.00% +2.66% -1.93% -3.16% -4.32% -2.15%

TABLE C-1: HRT and Bone Mineral Density: Selected Clinical Trials of 3 or Fewer Years (Page 7 of 7)

Study	Number of part pa	Duration of monitoring of bone d	Type of treatment	Results	
(1991)	13 placebo; 16 CEE; 20 medroxyprogesterone; 16 CEE/medroxyprogesterone	2 years	Patients were randomized into four groups: placebo; CEE 0.6mg; medroxyprogesterone 20mg; medroxyprogesterone 10mg/CEE 0.3 mg	Spine density:	
				CEE	2.10±1.50%
				Progest.	-4.58±1.30%
				CEE+progest.	0.88±2.58%
				Placebo	-7.22±2.39%
				Radial density:	
				CEE	-1.30±0.49%
				Progest.	-1.89±0.55%
				CEE+progest.	-0.05±1.06%
				Placebo	-4.12±2.07%
				Average cortical width:	
				CEE	-1.28±0.68%
				Progest.	-2.19±0.60%
				CEE+progest.	-2.24±0.58%
				Placebo	-6.53±1.11%
				Quantitative CT:	
				CEE	-3.64±2.36%
				Progest.	-10.1±3.01%
				CEE+progest.	-3.66±3.31%
				Placebo	-7.44±3.23%

SOURCE: Office of Technology Assessment, 1995.

TABLE C-2: HRT and Bone Mineral Density: Study Duration Greater Than 3 Years

Study	Number of participants	Study design	Duration of monitoring bone mass	Type of treatment	Results	
Meema, et al. (1 975)	29 control 53 treated	Retrospective cohort	4 to 10 years followup (6 years average followup)	Most frequently used hormone preparations were conjugated equine estrogens (0.625mg or 1.25 mg) usually administered cyclically	Castrates: Estrogen-treated Untreated Natural menopause: Estrogen-treated Untreated	+1.92% -7.78% +1.12% -6.30%
Lindsay, et al. (1978b)	14 controls; 15 treated 8 years; 14 treated, then treatment withdrawn	Clinical trial	8 years	Mean daily dose 27.6 mcg mestranol; 14 patients placebo; 14 patients 4 yrs. mestranol treatment then placebo 4 years; 15 patients received 8 years of mestranol treatment	Placebo group Estrogen group Estrogen, then withdrawal after 4 years	-11.9% -0.7% -10.070
Nachtigall, et al. (1979)	67 treated 62 controls	Clinical trial	10 years	Treated patients received CEE 2.5mg/day and 7 days each month medroxyprogesterone acetate 10mg.	<3 years from LMP: Estrogen-treated Placebo control >3 years from LMP: estrogen-treated placebo control	+8.67% ***-9.00%*** ***-0.5070*** -11.29%
Lindsay, et al. (1980)	42 control 58 treated	Clinical trial	Mean duration 9 years	Treated with mestranol mean daily dose 23.3mcg	Placebo: Metacarpal Radius Estrogen-treated: Metacarpal Radius	-10.4% -9.45% -1 .90% -2.1 5%

KEY: LMP = last menstrual period.

SOURCE: Office of Technology Assessment, 1995

who continued for a duration of at least 10 years. The mean duration of estrogen use among long-term estrogen users was 19.8 years. Controls were postmenopausal women who used estrogen for less than one year. There was a significant difference in mean spinal bone mineral density between long-term estrogen users (1.21 9 g/cm^2) and controls (1.092 g/cm^2), and this significant difference was retained after controlling for age and type of menopause.

In the only long-term prospective clinical trial of HRT and bone mineral density, 84 pairs of postmenopausal nursing home patients were randomly assigned to estrogen and progesterone or placebo (39). After 10 years, HRT-treated women had no significant decrease in bone mass. Women who began HRT within three years of menopause had a small **but** significant increase in bone mass after 1() years. Women assigned to placebo had a significant decrease in bone mass.

A number of studies have demonstrated that HRT is able to halt or possibly reverse bone loss even if it is started long after menopause (9,31, 32,35,41,43,45). Gains in bone mass of 5 to 10 percent or more have been found after initiation of HRT in the elderly. In a prospective study of 397 postmenopausal women between the ages of 51 and 80 years, Quigley found that estrogen replacement therapy reduced bone loss to about the same rate for estrogen users regardless of age (43).

Ettinger and Grady predicted that beginning therapy later in life may provide almost as much protection against osteoporotic fractures as starting at menopause (12). Ettinger and Grady used data on the effects of hormone replacement therapy on bone density, and the association of bone density to fracture risk to estimate and compare the expected benefits of three possible treatment scenarios: [1] 1) beginning therapy at menopause and continuing for the remainder of life; 2) beginning therapy at menopause and stopping at age 65; and 3) beginning therapy at 65 and continuing for the remainder of life (12). Their model included a number of key assumptions, based on their review of studies of the impact of hormonal replacement therapy in the elderly, including the assumption that bone mass would increase by 5 percent to 10 percent in the first two years after initiating therapy in the elderly. The investigators concluded that women who begin therapy at menopause and stop at age 65 have only a small (8 percent) increase in bone density at ages 75 to 85, the ages of highest hip fracture incidence, compared to never users, which translates into a 23-percent reduction in fracture incidence. Women who begin therapy at menopause and continue for the remainder of life were predicted to have the highest mean bone density at ages 75 to 85, about 22 percent higher than never users, and the greatest reduction in fracture incidence, a 73-percent reduction. But women who began HRT at age 65 had almost as great an increase in bone density, from 14 to 19 percent, and almost as great a reduction in fracture incidence, from 57 to 69 percent, as women who began HRT at menopause and continue for the rest of their lives.

Ettinger and Grady argued that starting hormone therapy later in life would halve the period of hormone exposure, reducing the potential risks of very long-term estrogen therapy (12).

There are several other reasons for beginning HRT in the elderly. Many of the early estimates of the rate of bone loss with aging were derived from cross-sectional studies, which may be biased if there are cohort effects. Recent prospective studies of bone loss with aging demonstrate that bone loss may accelerate with aging. Jones and colleagues reported on the rate of bone loss in 769 residents of Dubbo, Australia, aged 60 years and older, followed between January 1989 and June 1993. They found that bone loss at the hip was almost 1 percent per year in women, and about 0.8

[1] OTA's estimates of the impact of hormonal replacement therapy on fracture risk were calculated in a similar manner. See appendix D.

percent in men, and that bone loss increased with advancing age in both sexes (23).[2]

Recent data on the relation of bone mass to fracture risk in the elderly show that there continues to be a strong relationship of bone mass to hip fracture risk, even after age 80, so that therapies that slow bone loss will reduce fracture risk in this age group(3).

In addition, there is evidence from prospective studies that the rate of bone loss immediately after menopause may not be as great as previously thought, and the period of accelerated bone loss may not last as long as was predicted from cross-sectional studies (3). Finally, at age 65, densitometry can more precisely estimate the subsequent risk of hip fractures and target treatment more effectively (3).

There are, however, a number of reasons to question whether this type of model overestimates the number of fractures avoided by preserving bone mass in the elderly. Reports are inconclusive regarding how HRT initiated after substantial bone is lost affects fracture incidence (25). (See appendix B for discussion.)

In addition, progressive bone loss is associated with erosion and perforations in the trabecular structure, or struts, in cancellous bone (24,33). These perforations decrease the structural integrity of bone out of proportion to the amount of bone lost. Interventions such as estrogen that reduce bone resorption are at best capable of thickening the trabecular elements that remain, but are unlikely to be able to repair perforated trabeculae.

Finally, such a strategy would not be as effective in preventing wrist and vertebral fractures, which have a peak incidence earlier in menopause than hip fractures.[3]

After cessation of therapy, bone loss accelerates to a rate equivalent to that of untreated women at menopause (7,30,43). Thus, one would predict that the benefits of HRT on bone mineral density are maintained only so long as therapy is continued, and these benefits dissipate after cessation of therapy. Studies of bone mass in elderly women support this prediction. Felson and colleagues measured bone mass in 670 elderly women (mean age 76 years) in the Framingham study cohort to determine whether their bone mass was affected by earlier estrogen use (14). They found that, among the 212 women who had received estrogen therapy, only those who had taken estrogen for seven or more years had significantly higher bone mass than women who had not taken estrogen. The differences in bone mass between long-term users and nonusers was greatest among women under 75 years old (11.2 percent). Among long-term estrogen users 75 years old or older, bone density was only 3.2 percent higher than in women who had never taken estrogen around the time of menopause, and even those who had taken estrogen for 10 years had ceased therapy by the time they were 60 to 65 years old. Of the 24 women 75 years old or older who had taken estrogen therapy for at least seven years, only two had begun therapy at 60 years of age or later, and only three were still taking estrogen when their bone density was measured.

HRT has been found to reduce postmenopausal bone loss regardless of the route of administration (45,49,50). Lufkin and colleagues compared bone loss in 75 osteoporotic women randomly assigned to transdermal estrogen patches and progesterone tablets or to placebo patches and tablets (32). They found that bone mass was significantly greater in those who received the transdermal estrogen patch compared with those who received placebo. Those women receiving transdermal estrogen had a median annual increase in bone mass of 5.3 percent in the lumbar spine, compared to an increase of 0.2 percent for women receiving placebo. In a two-year clinical trial, Ribot and colleagues randomly assigned 94 postmenopausal women to a transdermal estrogen patch, a topically applied estrogen gel, or to a placebo (46). At the end of the

[2] They reported no significant bone loss at the spine, which was perhaps due to the presence of spinal arthritis (23).

3 Wrist fractures and vertebral fractures, however, cause relatively little morbidity compared with that incurred by hip fracture.

study, bone mineral density had increased significantly for the transdermal estrogen patch group and the percutaneous estrogen gel group, but not for the placebo group. There was no significant difference in the percent increase in bone density between the transdermal estrogen patch group and the percutaneous estrogen gel group.

The combination of estrogen and progestin, either given sequentially or as continuous combined therapy has been found as effective as estrogen alone in reducing postmenopausal bone loss (5,6,7,10,13,19,29,31,34,38,40,41 ,42,45,47,50).

In fact, a number of studies have demonstrated that progestins alone are effective in reducing bone loss in postmenopausal women (1,16,26, 29). Lindsay and colleagues demonstrated the ability of progestins to reduce bone loss in a clinical trial involving 30 postmenopausal women randomly assigned to the progestin gestranol, the estrogen mestranol, or placebo (29). Women treated with gestranol showed no significant change in bone mineral density after one year, and women treated with mestranol showed a nonsignificant increase in bone mineral density. Women assigned to placebo, however, showed a significant decline in bone mineral density after one year.

Abdalla and colleagues showed that progestin was able to increase bone mineral density in postmenopausal women in a cohort study of the progestin norethisterone versus placebo (l). Women assigned to norethisterone were referrals to a Glasgow, Scotland menopause clinic, and controls were patients chosen from placebo groups of other clinical trials matched to the treatment group for age, years since menopause, and initial bone mass. After two years, the bone mass of women assigned to norethisterone increased by 3.3 percent, whereas the bone mass of the matched controls declined by 5 percent. The difference in bone mass between the two groups after two years was statistically significant ($p < 0.002$).

Although progestins have been demonstrated to prevent bone loss in postmenopausal women, they do not appear to be as effective as estrogens in maintaining bone mass, especially mass of trabecular bone. Gallagher and colleagues randomly assigned 81 postmenopausal women to four groups: treatment with the progestin Provera R (medroxy - progesterone acetate), the estrogen Premarin (conjugated equine estrogen), Premarin plus Provera, or placebo (16). The group receiving Premarin plus Provera received half the dose of estrogen as the Premarin only group and half the dose of progestin as the Provera only group. After two years, bone mass of the spine (composed primarily of trabecular bone) was maintained in the Premarin group and the Premarin plus Provera group, but was lost in the Provera group and the placebo group. Bone density of the wrist (composed primarily of cortical bone) was lost in all four groups, but was least in the Premarin only, Provera only, and Premarin plus Provera groups, and was greatest in the placebo group. For both cortical bone and trabecular bone, Premarin alone was better able to maintain bone mass than Provera alone.

CONCLUSIONS

Controlled clinical trials have demonstrated that HRT is able to halt bone loss and perhaps increase bone mass in postmenopausal women. For this analysis, OTA has assumed as a base case that HRT maintains bone mass for as long as it is taken. There is less information about whether HRT is able to maintain bone mass over the long term. OTA also assumed that initiation of HRT at age 65 was able to maintain bone mass. Two recent reviews of studies of bone density have concluded that bone mass is lost in long-term HRT users, but at a rate that is one-half to one-third that of nonusers (3, 12). OTA assumed as a worst case that bone mass in HRT users is lost at half the rate of nonusers. Studies have demonstrated that bone loss is halted or reduced only as long as HRT is used. OTA assumed that, upon cessation of HRT use, bone mass is lost at a rate similar to the rate of bone loss at menopause.

Because there are relatively few data on the reduction of fracture in long-term estrogen users, OTA used data on the effects of HRT on bone density and the association of bone density on fracture risks to estimate the risks of hip fracture in HRT users at each age. This assumption is discussed in more detail in appendix D.

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Appendix D: Summary of Hip Fracture Prediction Methods

D

This appendix describes the assumptions used in OTA's analysis of the impact of hormone replacement therapy (HRT) on hip fractures.[1]

OTA's model assumes that HRT affects fracture risk through its impact on bone mass as measured by bone mineral density (BMD). The rationale for this assumption is twofold. First, the causal relationship between HRT and bone loss is well-established and precisely estimated, at least in the short-run. In contrast, the evidence of a direct relationship between HRT and fracture rests on studies with relatively weak designs that do not lend themselves readily to precise estimates of effect size. (See appendices B and C.) Second, the relationship between BMD measured at each age and the risk of hip fracture has been quantified in some recently reported studies.

REQUIREMENTS OF THE OTA HIP FRACTURE PREDICTION MODEL

OTA's model predicts the probability of hip fracture at every age between 50 and 90 as a function of an individual's BMD at age 50. The model is based on earlier work by Black and colleagues on the relationship between bone mass at menopause and lifetime risk of hip fracture (3). In that model, as in the present one, BMD at any age is predicted from BMD at menopause. (OTA used age 50 as a reasonable proxy for the age at menopause.) The predicted BMD at each age is then used to estimate the risk of fracture at that age.

The parameters required for such a model fall into two general categories: 1) those related to the longitudinal distribution of BMD; and 2) those relating BMD to the short-term risk of fracture. Most of the data available to estimate these relationships are based on studies of white women, the group at highest risk of osteoporosis and the only ethnic-sex group for whom data are available for estimations of sufficient precision for modeling. Where data on racial or ethnic groups or sexes other than white women are available, however, their findings are described in this appendix.

MEASURING BONE MASS

Different technologies are available for measuring bone mass at different sites in the body. How and

[1]This appendix is based on a contract report prepared in 1992 for OTA by Dennis Black (1). The data in that report reflected information available in 1992 .That report describes methods for predicting wrist, spine, and all fractures as well as hip fractures.

where bone mass is measured can affect its predictive power for hip fracture.[2] OTA's model is based on bone mineral density measured at the proximal radius (the lower forearm above the wrist) using single photon absorptiometry as the measurement technology. The primary reason for this choice is that the proximal radius is the only site for which there are sufficient data from a number of sources to make reasonable estimates of all parameters of the model. In particular, the proximal radius is the only site for which the longitudinal pattern of bone mass measurement over time has been characterized.[3] Because OTA's model requires consistent data on both changes in bone mass and the relationship between bone mass and fracture, no other site is feasible for modeling at present.

There has been some discussion in the literature about whether bone mineral content (gm/cm) (BMC) or density (actually areal density, gm/cm^2) is a better predictor of fracture risk. For predicting hip fracture, an analysis of data from the Study of Osteoporotic Fractures (SOF) showed that BMC was approximately the same as bone mineral density in predicting fracture (5). For predicting all fractures, other analyses performed on the SOF data have shown similar results. Although most studies have reported results in terms of BMD, some have reported BMC. This appendix treats these results as interchangeable, although the predictive model is measured in terms of BMD.

PREDICTING BONE MASS OVER TIME

The OTA model assumes that bone mass at any age follows a normal distribution with an age-specific mean and standard deviation. The evidence to support this assumption is summarized in the next section. If BMD at any age is normally distributed over the cohort of individuals in the age category, then the joint probability distribution of BMD at any two ages can be assumed to be bivariate normal. This implies that a woman's BMD at a given age, t, is related to her BMD at the previous age, *t* -1, according to the following formulas:

$$CMBMD_t = \mu_t + \rho_t (BMD_{t-1} - \mu_{t-1})$$

$$CSDV_t = \sigma_t^2 (1 - \rho_t^2))^{1/2}$$

$$BMD_t = Z * CSDV_t + CMBMD_t$$

where:

BMD = a woman's BMD at *age t;*

μ_t = the mean BMD in the population of women at age *t;*

σ_t = the standard deviation of BMD in the population of women at age *t;*

ρ = the correlation between a woman's BMD at age *t* and her BMD at age *t–1*.

$CBMD_t$ = the conditional mean of the probability distribution of BMD values at age *t* in women with BMD value at age *t–l* of BMD *t-l;*

$CSDV_t$ = conditional standard deviation at age *t;*

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2 Although a paper from the Hawaii Osteoporosis Center (29) has suggested that bone mass measurements taken at the calcaneus (heel) predicted all fractures better than did measurements taken at the radius (a bone of the lower part of the arm) or in the spine, the Study of Osteoporotic Fractures (the only other study which has measured bone mass at the calcaneus) has shown a relationship of approximately equal magnitude between bone mass and fracture risk at all sites (radius, calcaneus, spine and hip) for all fractures and for wrist fractures (3). For hip fractures, the three appendicular sites (proximal radius, distal radius and calcaneus) have been shown to be approximately equal as predictors (5) although recent data have suggested that bone mass at the proximal femur (thighbone) is abetter predictor of hip fracture risk than bone mass at the other sites (2,6). Unfortunately, no data on the longitudinal distribution of bone mass at the hip or the long-run predictive accuracy of any densitometry method are yet available.

3 After the proximal radius, the bone mass site studied most frequently is the spine. At present, however, the information available to estimate the parameters of the model are insufficient for three reasons. First, most studies of bone mass at the spine are either small, have a very wide age range, or have been performed on samples of women who are unrepresentative of the general population of women. Second, bone mass at the spine is measured by several techniques, including quantitative computed tomography, dual photon absorptiometry, and dual x-ray absorptiometry, each of which might show a unique longitudinal pattern or relationship to fracture risk. Third, as women age and develop anatomical abnormalities (e.g., vertebral deformities, osteophytes, etc.,) the spine presents special difficulties as a site for bone mass measurement.

TABLE D-1: Comparison of Observed to Predicted Percentile Values for Bone Mineral Density at the Proximal Radius (gm/cm^2)

	Age 65-76		Age 75-79	
Percentile	Predicted[a]	Observed	Predicted[a]	Observed
1	0.415	0.412	0.372	0.396
5	0.484	0.484	0.438	0,441
10	0.521	0.522	0.473	0.476
25	0.582	0.584	0.532	0.529
50	0.651	0.650	0.598	0,596
75	0.719	0.719	0.663	0,659
90	0.781	0.780	0.722	0,722
Mean (gm/cm^2)	0.6507		0.5978	
Standard deviation	0.1015		0.09705	

[a] Predicted values based on a normal distribution with the observed mean and standard deviation.

SOURCE: D. M. Black, "Cost Effectiveness of Screening for Osteoporosis' Review of Bone Mineral Density and Fracture Parameters Required for Model," University of California, San Francisco, CA, unpublished OTA contract report, Nov. 17, 1992

Z = a random number drawn from the standard normal distribution.

Thus, knowledge of the mean and standard deviation of the BMD distribution at each age, and the coefficient of correlation between the two distributions, permits the generation of a BMD trajectory for an individual woman over her lifetime.

This section reviews the evidence on the following aspects of the BMD prediction formula given above:

- Age-specific distribution of BMDs
- Correlation between BMD values at successive ages

Age-Specific Distribution of BMDs

The age-specific distribution of BMDs is defined by the general shape of the distribution (i.e., whether it is a normal, or bell-shaped curve, or defined by some other general form) and, if it is a normal distribution, its mean and standard deviation.

Shape of the BMD Distribution

Three large studies of bone mass are available to assess the shape of the BMD distribution.

- Study of Osteoporotic Fractures (SOF): The unpublished analysis in table D-1 compares the observed percentiles for bone mass at the proximal radius to the predicted percentiles based on a normal distribution. There is close agreement between the observed and predicted values, indicating that the normal distribution provides an excellent approximation to the observed, empirical distribution (1).
- University of Indiana: A study of bone mass in 583 women showed that the fit of bone mass data to a normal distribution was excellent (19). The investigators of this study have reported that they have found no evidence of significant skewing or other nonnormality in their cross-sectional data (15).
- University of Iowa: In a cross-sectional study of bone mass in 217 Caucasian women, bone mass variables were found to have a normal distribution (24).

These findings and the lack of any report suggesting that bone mass departs from a normal distribution, strongly suggest that at any age the distribution of bone mass across women is normal.

Age-Specific Means

Ideally, bone loss could be estimated directly from longitudinal data on cohorts of women followed for long periods of time. However, few such studies with sufficiently large numbers of subjects are

available. In the absence of such longitudinal data, bone loss can be estimated from age-specific means derived from cross-sectional data. OTA used a combination of longitudinal and cross-sectional studies to estimate change in bone mass with age.

It is possible to establish age-specific means from cross-sectional studies of bone mass in population-based samples of individuals, but there are a number of potential problems in using cross-sectional data to estimate longitudinal changes in bone mass.[4] First, the sample maybe biased. Second, the sample must be large enough in each age category to allow for sufficient precision. Third, cross-sectionally estimated changes in bone mass may differ from those estimated from longitudinal studies if there are cohort effects, such as nutritional factors or medication use patterns that vary with age.

Although many cross-sectional studies address the relationship of bone mass to age, most of these data are not very informative because they are from small studies without population-based samples. Two studies described in this section are exceptions.

Data from six separate studies of bone mass formed the basis for estimates of age-specific mean BMD. Each is described in detail below.

University of Indiana

A total of 268 women were studied longitudinally and 583 were studied cross-sectionally. They were recruited as two distinct samples. The cross-sectional sample was younger (under age 65) and consisted primarily of gynecology clinic patients and employees of the Indiana University Medical Center. The longitudinal sample consisted of a group of older subjects (over age 55, mostly over age 65) who were residents of a retirement home. The older women had repeated bone mass measurements (between three and 45, with a mean of 20 measurements) over followup periods ranging from six weeks to seven years (mean = 4 years). The samples have been used for a number of different analyses. The exact participants and measurements used have differed in the various reports of the study depending on the research question being addressed.

One analysis of these data compared longitudinal with cross-sectional estimates of mean BMC in post-menopausal women (19). This analysis showed that the cross-sectional results agreed closely with longitudinal results. The results showed a quadratic relationship between BMC and age which was essentially linear in the age range 50 to 70. The average rate of bone loss decreased after about age 70, and there is a suggestion of an increase in bone mass after age 70. The actual rates of loss in the data are not useful for the purposes of the OTA study, because they were adjusted for body weight without reporting enough information to calculate overall population means.

A more recent analysis of the same data looked in detail at bone loss in the period zero to five years after menopause and five to 10 years after menopause (18). The large number of repeat measurements over time gives very precise estimates of bone loss. For the period zero to five years after menopause, a total of 89 women were available for analysis with an average of 11 measurements during the five-year period. These women showed an average loss of about 1.6 percent per year over the five years. For the period five to 10 years after menopause, a total of 47 women were used with an average of eight measurements each during the five years. These women showed an average loss of about 1.2 percent per year over the five years.

University of Iowa

A sample of 217 Caucasian women from a rural community in Iowa between the ages of 22 and 80

4 Several studies have compared cross-sectional to longitudinal data sets for estimating bone loss with age (7,19). Only Davis and colleagues found the two approaches to lead to different results, although the methodology in their paper is difficult to interpret. Also, the data set which Davis used (a cohort of Japanese American women) may have cohort effects not present in other data sets.

TABLE D-2: Bone Loss by Age in the University of Iowa Cohort

Age at first measurement	Number of women	Percent loss per year
45-49	19	1.3%
50-54	36	2.0%
55-59	60	1.2%
60-64	55	1.2%
65-69	60	1.3%
70-74	43	1.2%
75-79	53	1.3%

SOURCE: M. Sowers, M. Clark, B. Hollis, et al., "Prospective Study of Radial Bone Mineral Density in a Geographically Defined Population of Postmenopausal Caucasian Women, " *Calcified Tissue International* 48:232-239, 1991.

had bone mass measured at the radius in 1984, and 181 of them had repeat measurements made five years later in 1989 (24,25). The strength of these data is that they were collected longitudinally over a long period of time (five years). However, the precision of estimates based on the data is limited due to the small numbers of participants. The average annual bone loss for women who were post-menopausal at the time of followup is given in table D-2.

For ages 50 and over, the confidence intervals around the mean percent loss are approximately plus or minus 0.3 to 0.4 percent. The loss rates in this study are approximately the same as other studies. There is an approximate doubling of the rate of loss during the five years after menopause.

University of Copenhagen

121 women who were six months to three years post-menopausal and who were 45 to 54 in 1977 had BMD measured in the forearm. Their BMD measurements were repeated 12 years later in 1989 (14). The mean loss averaged 1.7 percent per year over the 12 years.

Hawaii Osteoporosis Center

A cohort of 1,098 Japanese-American women, all post-menopausal, was established in 1981. This cohort has been extensively followed with repeat

TABLE D-3: Bone Mass by Age in Hawaii Osteoporosis Center Cross-Sectional Analysis

		BMC at the proximal radius	
Age	N	Mean (gm/cm)	Percent loss per year
43-49	11	.849	—
50-54	38	,797	1.2%
55-59	196	,790	1.2%
60-64	411	,745	1.1%
65-69	306	.687	1.2%
70-74	108	.669	0.5%
75-79	24	.577	2.7%

KEY BMC = bone mineral content

SOURCE K Yano, R.D. Wasnich, J.M. Bogel, et al , "Bone Mineral Measurements Among Middle-Aged and Elderly Japanese Residents in Hawaii," *American Journal of Epidemiology 119751-764,* 1984.

bone mass measurements. One analysis examined change in bone mass with age among post-menopausal women who did not use estrogen (7). These loss rates were adjusted for height, weight, and bone width. Longitudinal analyses (n = 636 women, mean length of followup = 3.2 years) in the same paper showed that the rate of loss was about 1.5 percent per year at age 55 and declined to about 0.8 percent at age 75. Cross-sectional analyses of bone density in 677 women showed a decrease in mean bone mass of approximately 1 percent for each year of age for women around the age of 55. The mean decrease by age increased to about 1.25 percent for each year of age for women around 75 years old.

The results of another cross-sectional analysis on the same sample, which *did not* exclude estrogen users, are shown in table D-3 (30). Through the early post-menopausal years, the results are essentially constant at about 1.2 percent per year. The results for age 70 to 74 are at odds with the remainder of the data and suggest either a typographic error (e.g., .699 should be .629) or imprecision due to small sample size.

An important caveat in interpreting analyses of these data is that the sample is drawn from a very special population (Japanese-American women

living in Hawaii) which may not reflect loss rates in a larger population. However, the general pattern of change in bone density with age is helpful in confirming the pattern found in other data sets.

Study of Osteoporotic Fractures

The largest cross-sectional study (9,704 women over age 65) of bone mass, the SOF should be reasonably representative of healthy white women over age 65 years in the U.S. (5). Data are available for bone mass measured by SPA in the proximal radius, distal radius and calcaneus, but only in women over the age of 65.

Steiger and colleagues recently reported an analysis of cross-sectional bone loss in SOF (26). However, that paper does not exclude current estrogen users. The data shown in table D-4 are the same as those in the Steiger paper but exclude estrogen users.

TABLE D-4: Mean Bone Mass by Age for Non-Estrogen Users in the Study of Osteoporotic Fractures

		Bone mass at the proximal radius	
Age	N	Mean (gm/cm^2)	Percent loss per year
65-69	1,864	.650	—
70-74	1,507	.620	0.9%
75-79	907	.598	0.7%
80-85	537	.566	1.O%
85-89	140	.541	0.9%

SOURCE:S.R. Cummings, D.M. Black, M C. Nevitt, et al , "Appendicular Bone Density and Age Predict Hip Fracture in Women, " *Journa/ of the American Medical Association* 263:665-668, 1990

Framingham Osteoporosis Study

The investigators in the Framingham study performed cross-sectional analysis of bone mass at various sites, including the proximal radius in 708 women over age 68 years. At the time of preparation of this report, no data had yet been published. However, preliminary results have suggested a constant loss rate of about 0.9 percent per year from ages 68 to 90 (1 ,13).

OTA's Estimate

Qualitatively, most studies have shown a slightly higher rate of bone loss at the appendicular sites just after menopause, which slows after about age 55 or 60. One interesting consistency among the data presented above is that the acceleration in bone loss just after menopause at these sites is only slight.

For the age range of 50 to 65, the various studies provide consistent results. The longitudinal data from Copenhagen suggest an average rate of loss of 1.7 percent per year for the 12 years after menopause. The Iowa data show a 1.6 percent loss for the five years after menopause with a 1.2 percent loss for the next five years. The estimated rates of loss from these three studies are quite consistent given the inherent imprecision due to limited sample size. Some of the discrepancies among the studies may also be due to differences in the study population, methods of analysis, or differences in measurement technique.

The only longitudinal study in the age range of 65 and over is the study from Iowa which showed a mean loss of about 1.2 percent per year. Two large cross-sectional studies are available of women over age 65 years. SOF is much larger than any other study and shows a constant rate of loss after 65 of 0.8 percent per year. The results from the Framingham study are consistent with those from SOF showing an average loss of about 0.9 percent per year after age 65.

Based on the results of these studies, OTA developed a base-case set of assumptions about the rate of change in mean bone mass of a population of women as they age. These assumptions are shown in table D-5. Alternative assumptions reflecting reasonable upper and lower bounds on the bone loss rate are also shown in the table.

In addition to the percentage of bone loss in each year, the OTA model requires an estimate of mean BMD at each age. Although all the studies described above are consistent in their estimates of loss rates, recorded bone density levels vary with each densitometer. Consequently, it is not possible to pool mean values from various

TABLE D-5: Assumptions About Bone Loss in OTA's Model

Age interval	Annual rate of loss		
	Base case	Slow loss	Fast loss
50-54	1.8%	1.6%	2.0%
55-59	1.3%	1.2%	1.5%
60-64	1.0%	0.9%	1.2%
>65	0.9%	0.8%	1.2%

SOURCE: Office of Technology Assessment, 1995.

TABLE D-6: Age-Specific Mean BMD (gm/cm^2) Under Various Assumptions About Bone Loss

Age	Assumption set		
	Base	slow loss	Fast loss
50	0.814	0.796	0.844
51	0.799	0.783	0.827
52	0.785	0.770	0.811
53	0.771	0.758	0.794
54	0.757	0.746	0.778
55	0.743	0.734	0.763
56	0.733	0.725	0.751
57	0.724	0.717	0.740
58	0.714	0.708	0.729
59	0.705	0.699	0.718
60	0.696	0.691	0.707
61	0.689	0.685	0.699
62	0.682	0.679	0.690
63	0.675	0.673	0.682
64	0.669	0.667	0.674
65	0.662	0.661	0.666
66	0.656	0.655	0.658
67	0.650	0.650	0.650
68	0.644	0.645	0.642
69	0.638	0.640	0.634
70	0.633	0.635	0.627
71	0.627	0.629	0.619
72	0.621	0.624	0.612
73	0.616	0.619	0.605
74	0.610	0.614	0.597
75	0.605	0.610	0.590
76	0.599	0.605	0.583
77	0.594	0.600	0.576
78	0.588	0.595	0.569
79	0.583	0.590	0.562
80	0.578	0.586	0.556
81	0.573	0.581	0.549
82	0.568	0.576	0.542
83	0.562	0.572	0.536
84	0.557	0.567	0.529
85	0.552	0.563	0.523
86	0.547	0.558	0.517
87	0.542	0.554	0.511
88	0.538	0.549	0.504
89	0.533	0.545	0.498
90	0.528	0.540	0.492

SOURCE: Office of Technology Assessment, 1995; D.M. Black, "Cost Effectiveness of Screening for Osteoporosis: Review of Bone Mineral Density and Fracture Parameters Required for Model, " University of California, San Francisco, CA, unpublished OTA contract report, Nov. 17, 1992.

sources. OTA used the estimated mean BMD value from SOF for ages 65 to 69 (0.650 gm/cm^2) as an *anchor* value for the age-specific BMD levels. The means at the other ages were calculated from this value at age 67 using the loss rates given in table D-5. The derived age-specific means are shown in table D-6 for the base assumptions and two alternative assumptions. Under the base assumption, there is an overall loss of 35 percent between ages 50 and 90. For the slow loss assumption set, there is an overall loss of 32 percent and under the fast loss assumption set, the overall loss is 42 percent.

Age Specific Standard Deviations

The requirements for estimating the standard deviations of the distribution of BMDs are similar to estimating their means: a large, randomly chosen sample in which estrogen users have been excluded. Longitudinal data are not required, however. Again, the problem of scaling of bone density values taken from different densitometers makes comparisons across studies difficult, and the values of a given study must be used as an anchor. An important question in analyzing the data available on standard deviation is whether it varies with age.

Because of its size and relatively representative sample, the SOF study provides the best estimates of standard deviation for women overage 65. Unpublished data from that study for women who have never used estrogen are shown in table D-7.

Although these data suggest that, at least for women over 65 years of age, the standard deviation is fairly constant, other studies suggest some variation with age. Data from the Indiana University sample of 268 post-menopausal women sug-

TABLE D-7: Age-Specific Standard Deviations of BMD in SOF (excludes women who have ever used estrogen)

Age	N	Standard deviation of bone mass (gm/cm^2)
65-69	1,864	.102
70-74	1,507	.100
75-79	907	.097
80-84	537	.096
85+	140	.095

KEY: BMD = bone mineral density; SOF = Study of Osteoporotic Fractures,

SOURCE: D. M. Black, "Cost Effectiveness of Screening for Osteoporosis: Review of Bone Mineral Sensity and Fracture Parameters Required for Model, " University of California, San Francisco, CA, unpublished OTA contract report, Nov. 17, 1992

gested that there is an *increase* in standard deviation with age, but no estimates of standard deviation were reported (19). Data from the University of Copenhagen study, on the other hand, showed a decrease in the standard deviation between the first measurement (age 45 to 54) and the second (age 57 to 66), by about 0.5 percent per year. The Framingham cross-sectional data also showed a decrease—about 0.6 percent per year-in women over age 68. The University of Iowa 1983 cross-sectional sample showed age-specific standard deviations of BMD that varied from a high of 0.119 gm/cm^2 (age 70 to 74) to a low of 0.081 gm/cm^2 (age 65 to 69). There was no clear trend with age, although the precision of the estimates is limited by the small numbers within each age group.

Estimates of standard deviations are less precise than estimates of means; it is therefore difficult to conclude from these data whether there is a real decrease in the variation of bone mass with age. In addition, the value of the standard deviation of bone mass depends on the technique used to measure bone mass as well as the population from which the sample was drawn. The data are most consistent with a slight decrease of standard deviation with age. However, the small decrease suggested would have a negligible effect on any results of the model. Therefore, OTA assumed that the standard deviation of bone mass at the proximal radius is 0.10 gm/cm^2 and does not change with age in the age range 50 to 90 years.

Correlation Between Values of Bone Mass at Two Ages

The model requires an estimate of the correlation between bone mass at the age at which BMD screening takes place and at later ages. For example, if screening for bone mass occurs at age 50, the model requires the correlation between bone mass at age 50 and bone mass at ages 51, 52, etc. The correlation required is the correlation between the true values of bone mass in successive years, not the measured values, because it is the true values that predict fracture. For long-term studies (e.g., at least five to 10 years), the correlation between the true values will be about the same as that between the measured values. However, in studies of shorter duration, measurement error plays a larger role artificially deflating the correlation.

The accuracy of the estimate of this model parameter is important, because changes in the estimates would have large effects on the resulting fracture rates. Fortunately, sufficient data exist (see below) to restrict its possible values, and within this range its effect on outcomes is only moderate.

To estimate the long-term correlation, longitudinal data must be collected over as long a period of time as possible. For example, to estimate the correlation between bone mass at age 50 and age 65, 15 years of followup data are needed on a cohort who were age 50 at the initial measurements. For the correlation between BMD at age 50 and BMD at age 80, a 30-year followup period is necessary. The ideal data set would have bone mass measured on a large random sample of women from the age of 50 to 90. Clearly, such data do not (yet) exist.

Three studies have reported the correlation between bone mass measurement at widely separated intervals. The University of Indiana analysis of post-menopausal women estimated the correlation between bone mass measured within two

years of age 50 with bone mass measured about 10 years later based on the experience of 34 women (18). The data showed a correlation of about 0.81 between measurements taken at ages 50 and 60 and a correlation of about 0.7 between measurements made at ages 50 and 70.

For women over age 55, the University of Iowa study found that the correlation between the two measurements taken five years apart was greater than 0.9 (24). However, the exact 5-year correlation was not given.

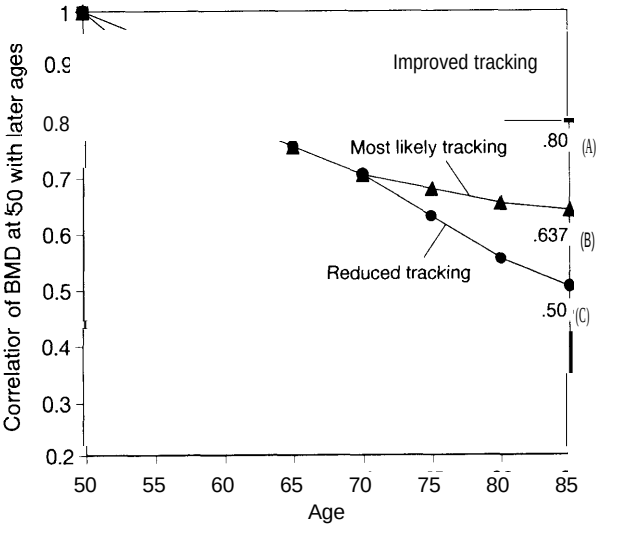
Finally, in the University of Copenhagen study of 121 post-menopausal women aged 45 to 54 at entry, the correlation between the first measurement and the second taken 12 years later was 0.8 (95 percent CI: 0.7 to 0.9) (14).

The two long-term data sets on early post-menopausal women agree closely in showing a 10-year correlation of about 0.8. OTA used this value as the base assumption about the longitudinal correlation from age 50 to age 60. For ages 50 to 70, we used the estimate of 0.7 from the University of Indiana. Beyond age 70, for the base assumption, a quadratic function was fit under the assumption that the degradation in correlation continues after age 70 in the same pattern as before age 70.

Alternative assumptions are possible. Figure D-1 shows three alternative correlation trajectories. Under the base-case assumptions, the extrapolation of correlation beyond age 70 (pattern B in figure D-1) continues to decrease along the same quadratic pattern as before age 70. As a woman ages and becomes less active and more ill, however, a second acceleration in bone loss may occur. Since this increased bone loss would be associated with factors that could not be predicted from bone mass at age 50, a decreased correlation between bone mass at age 50 and bone mass beyond age 65 would result. Pattern C represents the decreased correlation that might be associated with increased bone loss associated with severe immobility and/or illness or extreme old age.

Another correlation trajectory (pattern A in figure D-1) maps a correlation of bone mass at each age with bone mass at age 50 that is higher than the base-case pattern. This might occur if a more precise measurement of bone mass was made.

FIGURE D–1: Three Patterns of Correlation Between BMD at Age 50 and BMD at Later Ages

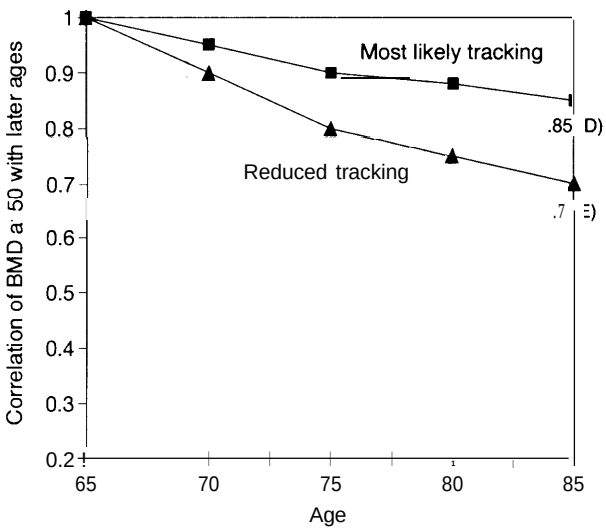


SOURCE D.M. Black, "Cost Effectiveness of Screening forOsteoporosis: Review of Bone Mineral Density and Fracture Parameters Required for Model," University of California, San Francisco, CA, unpublished OTA contract report, Nov 17, 1992

There is little published data specifically addressing the correlation between bone mass at age 65 and later ages. However, the correlation of bone mass between age 65 and subsequent ages will almost certainly be better than correlations with age 50, because a relatively high rate of perimenopausal bone loss after age 50 adds greater variability to predicting later values. Thus, the correlation between bone mass at age 65 and ages above 65 will almost certainly be higher than the correlation between bone mass at age 50 and later ages.

Because the OTA model uses year-to-year correlation estimates, the estimates projected in figure D-1 probably represent too steep a loss of correlation in later years. Consequently, we revised the correlation pattern after age 65 to account for the higher correlation pattern at older ages. Figure D-2 contains the results. Pattern D represents a correlation after age 65 that is slightly

FIGURE D–2: Two Patterns of Correlation Between BMD at Age 65 and BMD at Later Ages



SOURCE: D. M. Black, "Cost Effectiveness of Screening for Osteoporosis: Review of Bone Mineral Density and Fracture Parameters Required for Model," University of California, San Francisco, CA, unpublished OTA contract report, Nov. 17, 1992,

higher than that assumed after age 50 (pattern B in figure D-l). This pattern was used as the base-case assumption. Pattern E is analogous to the data from Hui for peri-menopausal women showing a correlation of 0.90 after five years (at age 70), a correlation of 0.80 after 10 years, etc. This pattern probably represents a lower limit on the correlation of bone mass after age 65 (18).

The OTA model requires correlations between bone mass at each age and bone mass at the next highest age. The patterns above include only the correlation between age 50, or age 65, and subsequent ages. However, the cost-effectiveness model requires the correlation between, for example, bone mass at ages 60 and 65 and between ages 80 and 85. We required a pattern of short-term correlations that approximates the long-term correlations shown in the figures above.

To approximate the long-term pattern in the base-case (pattern C in figure D-1) we assumed that the correlation between bone mass at any age and subsequent bone mass five years in the future is 0.90 forages 50 to 60 and 0.95 for ages over 60. If the correlations follow an autoregressive model, then the correlations between any two points can be found simply by multiplying the correlations in between. For example, the correlation between age 50 and 60 is 0.9 x 0.9 or 0.81. Under the autoregressive model, the long-term pattern closely approximates pattern C. Similar sets of short-term correlations could be developed for the other long-term correlation patterns above.

RELATIONSHIP OF BONE MASS TO HIP FRACTURE RISK

At any age, the OTA model must predict the probability of hip fracture as a function of the woman current BMD. Following work of Black and colleagues, OTA assumed a logistic relationship between BMD and hip fracture risk (4). A logistic is given by the following formula:

$$P = \frac{1}{1 + e^{\alpha_t + \beta_t x}}$$

where:

P is the probability of hip fracture at a given age;

α is a constant term that varies with age;

β is a term that varies with BMD, but not with age; and

x is the individual's BMD at the age in question.

When the risk of fracture is less than about 10 percent (as is the case for all hip fracture risks considered in this appendix), the logistic relationship between bone mass and risk is essentially linear. Therefore, data fitted to any other functional form that is similarly linear would yield essentially the same results as those obtained from fitting data to estimate the parameters (α,β) of the logistic model. However, if a nonlinear relationship (e.g., threshold model) were the true relational form between BMD and hip fracture, the logistic assumption would yield substantially erroneous results. It is therefore important to establish the validity of the logistic (or linear) relationship.

There is only one source of data (SOF) that has published data relating bone mass to risk of hip fracture (5). The results of that analysis suggest that the relationship of bone mass to hip fracture

TABLE D-8: Relationship of Proximal Radius Bone Mass to Non-Spine Fracture in SOF

Age group	N	Fractures	SD	RR[a]	95% CI
65-74	6,896	934	0.10	1.36	(1 .27,1 .45)
75+	2,441	470	0.10	1.33	(1 .21,1 .47)

[a]Relative hazard per standard deviation decrease in bone mass.

SOURCE: D. M. Black, "Cost Effectiveness of Screening for Osteoporosis' Review of Bone Mineral Sensity and Fracture Parameters Required for Model," University of California, San Francisco, CA, unpublished OTA contract report, Nov. 17, 1992

risk follows a linear pattern and that the logistic model is therefore a consistent description of the true relationship. A statistical test for the goodness of fit of the data to a logistic model did not reject the null hypothesis that the relationship is logistic.

The relationship between bone mass and fracture probability is usually estimated in terms of a standardized relative risk: the ratio of risk of a person whose bone mass is one standard deviation below the mean to the risk of a person whose bone mass is at the mean.

A critical assumption of the OTA model is that the relative risk of fracture is constant across age groups (or, alternatively, that β is constant across all age groups). For example, if the relative risk of fracture of a 70-year-old woman whose BMD lies 1 standard deviation below the mean BMD of 70-year-old women is 3, then the relative risk of a 50-year-old woman with BMD at 1 standard deviation below mean BMD of 50-year-old women is also 3. This assumption is equivalent to stating that there is no interaction between bone mass and age in predicting hip fractures. Virtually all published analyses in this field have included this assumption (e.g., 3,5,1 1,12,17,22,28).

Fortunately, data available to test the interaction between bone mass and age suggest that the assumption is valid. Table D-8 shows data provided by the SOF on the relationship of BMD (measured in the proximal radius) to hip fracture risk in ages 65 to 75 compared with ages 75 and over. There is a very slight suggestion of decreasing strength in the relationship of bone mass to hip fracture risk with increasing age. However, the large overlap in the two confidence intervals shows that the differences do not approach statistical significance. A recent analysis of SOF data of radical BMD prediction of hip fracture found no difference between women over 80 years of age and those under 80 years of age (23). Therefore, OTA assumed that the relative risk relating to bone mass and hip fracture risk is constant across all ages in the model.

Relative Risk of Bone Mass and Hip Fracture

Several sources of data are available on the short-run risk of hip fracture as a function of bone mass.

SOF published data using bone mass at three sites to predict hip fracture in the sample of 9,704 women (5). The average followup was 1.7 years. The standardized age-adjusted relative risk for BMD (gm/cm^2) at the proximal radius was 1.4 (1.1 to 1.9). Analysis using BMC as the measure found slightly lower relative risks.

The University of Indiana reported on a total of 23 first hip fractures in 135 residents of a retirement home (17). Bone mass (gm/cm^2) at the proximal radius was used as the predictor of hip fracture. The relative risk (95 percent CI) was 1.9 (1.3, 2.8) per 0.1 gin/cm of BMC (approximately 1 SD). Age was not a significant predictor of hip fracture after adjustment for BMC.

An analysis of the data on 1,076 women in Malmo, Sweden, found that after adjusting forage, the relative risk was 1.8 (95 percent CI: 1.3 to 2.4) for BMC of the mid-radius. However, since these findings were not age-adjusted, they overestimate the age-specific relationship of bone mass to risk and therefore may not be of direct relevance to this study. (20,2 1). A recent analysis of a cohort of 304 women in Rochester, Minnesota, who were fol-

TABLE D-9: Annual Incidence of Hip Fracture in White Women, 1983

Age	Annual incidence of hip fracture (per 100.O00)
50-54	69.5
55-59	135.4
60-64	169.6
65-69	314.3
70-74	493.5
75-79	1,033.2
80-84	1,669.3
85-89	2,552.5

SOURCE M.E. Farmer, L R., White, J, A., Brody, et al., "Race and Sex Differences in Hip Fracture Incidence, " *American Journal of Public Health* 74:1374-1380, *1984.*

lowed for an average of eight years, found a standardized relative risk of hip fracture of 2.7 (95-percent CI: 1.5 to 5.0) (21).

Black and colleagues performed a meta-analysis to calculate a pooled estimate and confidence interval for the relative risk of hip fracture forage-adjusted levels of bone mass in the radius, the only measurement site that was common to all three studies (4). Standard meta-analytic methods permit estimation of a pooled treatment effect and confidence intervals for data from numerous clinical trials (10). This pooled relative risk is calculated as the weighted mean of the individual standardized relative risks from each study, using the squares of the inverse of the standard error of the relative risk as the weights. The resulting combined relative risk was 1.65, with a 95 percent confidence interval of between 1.4 and 2.0. On the basis of this meta-analysis, OTA used a value of 1.65 as the base assumption for relative risk of hip fracture.

▮ Calculation of the Constant Term for the Logistic Model

We have assumed that the relative risk relating bone mass to fracture is the same for all age groups. The absolute risk of fracture does increase with age, however. The constant term in the logistic model, *a,* must be estimated for each age to adjust the absolute risk for differences in age.

TABLE D-10: Logistic Parameters for Hip Fractures in OTA's Hip Fracture Model

Relative risk per standard deviation	1.65
Corresponding value of beta (6)	-5.0078
Values of alpha *(a)*	
Bone loss = base case assumption	
Age	**Value of** *a*
50-54	-3.465
55-59	-3.10272
60-64	-3.0874
65-69	-2.62888
70-74	-2.32062
75-79	-1,70997
80-84	-1.35219
85-89	-1.04624
Bone loss = slow	
Age	
50-54	-0.2460
55-59	-0.2283
60-64	-0.2870
65-69	-0.2533
70-74	-0.3520
75-79	-0.3655
80-84	-0.1783
85-89	-0.3261
Bone loss = fast	
Age	
50-54	-3.3348
55-59	-3.0226
60-64	-3.0473
65-69	-2.6289
70-74	-2.3657
75-79	-1.8001
80-84	-1.4824
85-89	-1.2015

SOURCE: Off Ice of Technology Assessment, 1995, D M Black, "Cost Effectiveness of Screening for Osteoporosis Review of Bone Mineral Density and Fracture Parameters Required for Model, " University of California, San Francisco, CA, unpublished OTA contract report, Nov. 17, 1992.

Under the assumption of an age-invariant relative risk, the constant term can be estimated using age-specific hip fracture incidence data (i.e., no age-specific data on the relationship of bone mass

to fracture is required). This method has been described elsewhere (4).

Briefly, the overall age-specific incidence of fracture ($P(F_t)$) is the mean of the bone-mass-specific incidence ($P(F_t|BM_t)$) weighted by the age-specific distribution of bone mass $f(BM_t)$ or:

$$P(F_t) = \int P(F_t|BM_t)\, f(BM_t)\, dBM_t)$$

If we have data on the age-specific incidence of fracture and on the age-specific distribution of bone mass (both of which are readily available from cross-sectional studies) and we know the relative risk parameter (β) for the logistic model, the only unknown in the logistic function equation is the parameter α_t.

OTA used data from the National Hospital Discharge Survey to estimate the age-specific incidence of hip fracture (8). Table D-9 shows those incidence estimates. Other population-based studies have yielded similar annual incidence rates of hip fracture among white women (9,27). Based on these data, the values of the parameters *a* and β in the logistic function are as given in table D-10.

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Appendix E: Hormonal Replacement Therapy Regimens

E

The proportion of post-menopausal women who use hormone replacement therapy (HRT) has increased in the United States during the last two decades (13). While use of HRT has increased, the average dose and duration of use of postmenopausal estrogens has decreased until recently (64). This is due in part to the discovery that the cancer-causing effects of postmenopausal estrogen are related to its dose and duration.

This appendix describes the range of choice regarding the dose, routes of administration, and combinations of hormones currently in use or under study as treatment for postmenopausal HRT. This appendix also describes the appropriate follow-up of women on HRT. Finally, this appendix describes how dosing regimens may affect compliance with HRT and describes other factors that affect HRT compliance.

HRT involves the administration of estrogen alone or in combination with progestins. In the past, estrogen was typically administered without progestin (unopposed estrogen) in estrogen replacement therapy (ERT). Currently, the most commonly used regimens for a woman with a uterus include a progestin either in sequence with estrogen (e.g., 25 days of estrogens with a concurrent progestin administered during the last 12 to 14 days and a three-day drug-free period) or in continuous combination with estrogen. These progestin/estrogen therapies (PERTs) alter the benefit-risk profile of HRT.

In the United States, conjugated equine estrogen (CEE) (Premarin, Wyeth-Ayerst) is the most commonly used form of estrogen for HRT.[1,2] There are a number of other estrogens used for HRT.[3] Table E-1 lists the estrogens either approved for osteoporosis by the Food and Drug Administration or accepted for this use by a committee of the United States Pharmacopoeia. In addition to the estrogens listed in the table, the estrogens quinestrol (Estrovis tablets, Parke-Davis) and chlorotrianisene (TACE capsules, Marion Merrel Dow) are approved by the FDA for treatment of menopausal symptoms (61).

ESTROGEN DOSING REGIMENS

A central question for clinical management of postmenopausal HRT patients is how small a dose of estrogen may be administered without losing the beneficial effects of the therapy. The reduction in bone loss or menopausal symptoms must be weighed against the adverse effects of estrogens. The higher the dose of estrogen, the more likely are side effects, such as breast tenderness or fluid

retention (15, 27, 28).[4] In addition, higher doses may increase the risk of estrogen-related illness such as endometrial cancer or gallbladder disease.

Several studies have demonstrated that doses of at least 0.625 mg per day of CEE or its equivalent are necessary to prevent or greatly reduce bone loss in the spine in peri- or postmenopausal women (36,46,72). Lower doses offer only partial protection against bone loss (46,47). The minimal dosage of estrogen adequate to prevent bone loss in postmenopausal women is discussed in greater detail in appendix C.

The American College of Obstetricians and Gynecologists recommends the following estrogen dosages for osteoporosis (l):

Estrogen	Dose
conjugated estrogen	0.625 mg/day
transdermal estradiol	0.05 mg twice a week
micronized estradiol	1.0 mg/day
estrone sulfate	1.25 mg/day

For women who have not had hysterectomies, ACOG recommends the addition of a progestin to the estrogen. They recommend a dose of 10 mg/day for 12 days a month to reduce the incidence of hyperplasia and endometrial cancer. ACOG and the American College of Physicians see no reason to add progestin to estrogen for a woman without a uterus.

Routes of Administration

There are a number of routes for delivery of estrogens other than by mouth. Intramuscular injections have been tested, but they are no longer used, not only because they are uncomfortable but also because estrogen plasma concentrations are unstable with this method of administration (68). Vaginal rings and vaginal creams have also been investigated (53,63), but plasma estrogen levels are unstable, probably because of irregular ab-

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[1] There are currently no generic forms of conjugated estrogens on the market, but there are generic forms of some of the other estrogens used for postmenopausal replacement therapy. In 1989, the Center for Drug Evaluation and Research of the FDA rejected applications for new drug approval submitted by Barr Laboratories for five dosage strengths of generic conjugated estrogen (7). Although the extent of absorption of the estrogen was the same as that of Premarin, the brand-name drug manufactured by Wyeth-Ayerst, the FDA ruled that the generic manufacturer must demonstrate that the *rate* of absorption must be the same in order for the generic products to be considered bioequivalent to the innovator drug. Barr Labs claimed that this was inconsistent with a January 1989 determination by the FDA's Fertility and Maternal Health Drugs Advisory Committee that the rate of absorption was not relevant to bioequivalence (7).

Although a few members acknowledged that there was no conclusive evidence that the rate of estrogen absorption is important in determining the safety and efficacy of conjugated estrogens, the FDA's Generic Drugs Advisory Committee concluded in February 1991 that the rates of absorption must be the same to establish bioequivalence (16). The FDA contended that different absorption rates could make conjugated estrogens ineffective in treating osteoporosis. In addition, more rapid absorption of estrogen into the blood stream could lead to higher peak drug plasma concentrations which could increase the risk of endometrial cancer (30).

At present, sponsors of generic conjugated estrogen products are required to perform studies of the blood concentration-time profiles of five of the predominant estrogens in Premarin brand of conjugated equine estrogen (4). As of 1995, there were no generic conjugated estrogens on the market, although the generic manufacturer Duramed had an ANDA pending for a 0.625 mg formulation (4). Wyeth-Ayerst, manufacturer of Premarin brand of conjugated estrogen, has argued that a conjugated estrogen product that does not also contain a sixth form of estrogen, delta(8,9)-dehydroestrone, is not substantially equivalent to Premarin.

[2] *Data from Wyeth-Ayerst,* manufacturers of the most widely prescribed postmenopausal estrogen, show that three types of physician specialists — obstetrician-gynecologists, internists, and family-practitioners — wrote 90 percent of estrogen prescriptions. Obstetrician-gynecologists prescribe the most, with 2,897,000 prescriptions, or 43 percent of prescriptions for postmenopausal estrogens.

[3] *The estrogens used in hormone replacement* therapy are much less potent than the synthetic estrogens used in oral contraceptives. Because of this difference in potency, the side effect profile of estrogens used in hormonal replacement therapy differs from that of estrogens used for contraception.

[4] Fibroid tumors and endometriosis may also be exacerbated by HRT. Fibroids and endometriosis are both estrogen-dependent conditions that regress at menopause. HRT in postmenopausal women who had significant problems from either of these diseases premenopausally requires careful surveillance: fibroids may enlarge, and endometriosis maybe reactivated. If HRT is subsequently discontinued, the fibroids will again shrink. However, the sequelae of endometriosis, such as chocolate cysts or adhesions, may persist even after estrogen has been withdrawn, and continue to cause symptoms (20).

TABLE E-1: Estrogen Products Available in the U.S. for Osteoporosis (Page 1 of 2)

Generic name	Brand name (t.m.)	Manufacturer	FDA-approved indications	Recommended dosages for osteoporosis and/or menopausal symptoms[a,b]
Conjugated equine estrogen	Premarin tablets	Wyeth-Ayerst	1) Moderate to severe vasomotor symptoms of menopause 2) Vaginal or urethral atrophy 3) Osteoporosis 4) Hypoestrogenism due to castration, hypogonadism, or primary ovarian failure 5) Breast cancer 6) Prostatic carcinoma	Menopausal symptoms: 0,625 mg to 1.25 mg a day cyclically or continuously Osteoporosis: 0.3 mg to 1.25 mg a day, cyclically or continuously
Diethylstilbestrol (DES)'	Diethylstilbestrol enteric-coated tablets[d] Diethylstilbestrol tablets[d]	Lilly	1) Breast cancer 2) Prostatic carcinoma	Neither the USP DI nor the product labeling includes dosage information for osteoporosis or menopausal symptoms.
Esterified estrogens	Estratab tablets Menest tablet	Solvay SmithKline Beecham	1) Moderate to severe vasomotor symptoms of menopause 2) Vulvar or vaginal atrophy 3) Hypoestrogenism due to hypogonadism, castration, or primary ovarian failure 4) Breast cancer 5) Prostatic carcinoma	Menopausal symptoms: 0,625 mg to 1.25 mg, cyclically or continuously
Estradiol	Estrace tablets Emcyt capsules	Bristol-Myers Squibb Pharmacia Adria	1) Osteoporosis 2) Moderate to severe vasomotor symptoms of menopause 3) Vulvar or vaginal atrophy 4) Hypoestrogenism due to hypogonadism, castration, or primary ovarian failure 5) Breast cancer 6) Prostatic carcinoma	Menopausal symptoms: 0.5 mg to 2 mg a day, cyclically or continuously Osteoporosis: 0.5 mg a day, cyclically or continuously

TABLE E-1: Estrogen Products Available in the U.S. for Osteoporosis (Page 2 of 2)

Generic name	Brand name (t.m.)	Manufacturer	FDA-approved indications	Recommended dosages for osteoporosis and/or menopausal symptoms[a,b]
Estradiol transdermal system	Estraderm	Ciba	1) Osteoporosis 2) Moderate to severe vasomotor symptoms of menopause 3) Vulvar or vaginal atrophy 4) Hypoestrogenism due to hypogonadism, castration, or primary ovarian failure	Osteoporosis or menopausal symptoms: One transdermal dosage system delivering 0.05 mg or 0.10 mg, per day worn continuously and replaced twice a week
Estropipate	Ogen tablets Ortho-est tablets	Upjohn Ortho	1) Osteoporosis[e] 2) Moderate to severe vasomotor symptoms of menopause 3) Vaginal or vulvar atrophy 4) Hypoestrogenism due to hypogonadism, castration, or primary ovarian failure	Menopausal symptoms: 0.75 mg to 5 mg estropipate per day, cyclically or continuously Osteoporosis: 0.75 mg per day for 25 days of a 31-day cycle
Ethinyl estradiol[c]	Estinyl tablets	Schering	1) Moderate to severe vasomotor symptoms of menopause 2) Hypogonadism 3) Prostatic carcinoma 4) Breast cancer	Menopausal symptoms: 0.02 mg of 0.05 mg per day, cyclically or continuously

[a]Dosages are for vasomotor symptoms of menopause.
b Dosages were those recommended in the USP DI, See the United States Pharmacopeial Convention, USP *Dispensing Information* (USP DI): *Volume 1—Drug Information for the Health Care Professionl* (Taunton, MA Randy McNally, 1995).
[c]A U.S. Pharmacopeia Advisory Committee has accepted osteoporosis as an unlabeled indication for this product. An indication for postmenopausal osteoporosis, however, is not included in the FDA-approved labeling for this product See The United States Pharmacopeial Convention, *USP Dispensing Information (USP DI): Volume 1—Drug Information for the Health Care Profession/* (Taunton, MA Rand McNally, 1995).
[d]Diethylstilbestrol is available only as a generic In the United States.
[e]The FDA-approved labeling of Ortho-est (Ortho) brand of estropipate does not include an indication for osteoporosis
Key: CEE = conjugated equine estrogen, HRT = hormone replacement therapy, t m = trademark

SOURCE: Office of Technology Assessment, 1995

sorption due to day-to-day changes in vaginal blood flow and secretion.

Implantation of continuously released estrogen under the skin (subcutaneous implantation) appears to result in stable estrogen levels (68). But once inserted, the implants are difficult to remove in case of overdose or intolerance (76).

Administration of estrogen through a patch or cream applied to the skin (percutaneous transdermal administration) has proved effective in treating postmenopausal symptoms (14,22) and in reducing vertebral bone loss after menopause (72).

Transdermal medication may increase compliance because it eliminates the need for multiple dose scheduling, is easily administered, requires only twice weekly application, and is reversible (78). However, the gel is difficult to administer accurately (68). Absorption is proportional to the surface of application, and this surface cannot be determined accurately. In addition, between 5 and 20 percent of women may develop skin irritation (79).

THERAPY WITH PERT

The primary indication for adding progestins to estrogen replacement therapy is to reduce the risk of estrogen-induced irregular bleeding, endometrial hyperplasia (abnormal overgrowth of the inner lining of the uterus, or endometrium), and endometrial cancer (26,87). (See appendix G). In the Postmenopausal Estrogen/Progestin Interventions (PEPI) study, almost half of the women assigned to unopposed estrogen therapy experienced endometrial hyperplasia over the two year clinical trial (91); the PEPI trial protocol required that these women be taken off of estrogen. Because of the unexpectedly large proportion of women on ERT who developed hyperplasia in PEPI, the directors of the Women's Health Initiative long-term clinical trial of hormonal replacement therapy decided to place all women assigned to unopposed estrogen on PERT.

A number of progestins can be used for PERT.[5] The most commonly used progestin in the United States is medroxyprogesterone (Provera, Upjohn). In addition, the FDA has recently approved a combination of medroxyprogesterone acetate and conjugated equine estrogen for the prevention of osteoporosis. (See table E-2.)

Progestins produce progressive endometrial atrophy, converting adenomatous hyperplasia to normal endometrium (85). Numerous studies show that combined estrogen/progestin therapies can return 98 to 99 percent of preexisting hyperplasia back to normal endometrium (32,73). (See appendix G.) Observational studies also show that PERT users have a lower risk of endometrial cancer than ERT users (42).

An important unresolved issue regarding PERT is whether the benefits of progestins in protecting the endometrium are outweighed by the effect of progestins on the risk of coronary heart disease (CHD). Epidemiologic studies of the relationship of HRT to CHD have been largely limited to unopposed estrogens; the effect of progestin supplementation on heart disease risk has not been as extensively evaluated, but recent evidence suggests that adding progestins to HRT may attenuate the beneficial effects of ERT on heart disease. (See appendix I.)

Progestins are more often responsible than estrogen for making hormonal replacement therapy unacceptable for some women, because adverse effects are common with progestins (71). Progestins can produce breast tenderness, bloatedness, edema, abdominal cramps, and an iatrogenic premenstrual-like syndrome (71,87). Patients also commonly experience side effects such as anxiety, irritability, depressed mood, and drowsiness.

One of the primary reasons for stopping HRT is discomfort with periodic bleeding (18). With sequential therapies, regular bleeding occurs with 85 percent of patients (31,87). This proportion decreases with time, and by age 65, 60 percent continue to experience light bleeding (33). Patients

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5 Synthetic Progesterone are often used in hormonal replacement therapy since natural progesterones cannot be absorbed orally.

TABLE E-2: Progestins Products Available in the U.S. for Use with Estrogen in Osteoporosis

Generic name	Brand name (tin.)	Manufacturer	FDA-approved indications	Recommended dosage for secondary amenorrhea[b]
Medroxyprogesterone acetate	Amen Curretab Cycrin Provera	Carnick Solvay Esi Pharma Upjohn	1) Secondary amenorrhea 2) Abnormal uterine bleeding	Secondary amenorrhea. May be given in dosages of 5 to 10 mg daily for from 5 to 10 days.
Norethindrone acetate	Aygestin Norlutate	Esi Pharma Parke-Davis	1) Secondary amenorrhea 2) Endometriosis 3) Abnormal uterine bleeding	Secondary amenorrhea: May be given in dosages of 2.5 to 10 mg daily for 5 to 10 days during the second-half of the theoretical menstrual cycle.

[a] A U.S. Pharmacopeia Advisory Committee has determined that osteoporosis is an accepted indication for these products. An indication for osteoporosis, however, is not included on the FDA-approved labeling for these products See The United States Pharmacopeial Convention, *USP Dispensing Information (USP DI): Volume 1—Drug Information for the Health Care Professional* (Trauton, MA: Rand McNally, 1995)
[b] The **FDA-approved product labeling does not have** dosage recommendations for use Of these products with estrogen in Osteoporosis
KEY: t.m. = trademark
SOURCE Off Ice of Technology Assessment, 1995

may be willing to tolerate bleeding for relief of menopausal symptoms, but to an asymptomatic woman in her 60s and 70s who is taking estrogens for the prevention of osteoporosis and cardiovascular disease, the persistent bleeding and other side effects may be intolerable (26).

Compliance may be improved with new continuous combined regimens of PERT that reduce the frequency of menstrual bleeding. Continuous PERT involves daily administration of estrogen and a low dose of progestin (70). Several studies show that continuous PERT can relieve menopausal symptoms, eliminate periodic bleeding within several months of initiation, and avoid endometrial hyperplasia (5,28,37,40,48,70,84,91).

Most studies to date have found between one-third and one-half of patients were bleeding after three months of continuous PERT, but most patients were amenorrheic after 12 months. And most studies reported 90 percent or greater atrophic endometrium at 12 months.

Another approach to reduce the frequency of bleeding and improve compliance is to give sequential PERT with less than monthly progestin therapy. For example, Williams and colleagues found that that there was less vaginal bleeding when progestins were administered for 14 days every three months than when given for 14 days every month (90). Menopausal women find less than monthly bleeding more acceptable than monthly bleeding (6).

ACUTE INDICATIONS FOR HRT

The most common indication for HRT is relief of menopausal symptoms (41).[6] Hot flashes, or vasomotor symptoms, are the most common symptom of menopause that causes women to seek medical attention (81). Hot flashes occur in 60 to 75 percent of women at the time of menopause (52,82). They are typically more severe in women with surgical menopause, because the severity of

6 The American College of Physicians distinguishes between diagnoses for short-term and long-term HRT (3). Short-term HRT is prescribed for women who suffer from postmenopausal symptoms, such as hot flashes and atrophic vaginitis. The American College of Physicians suggests therapy of one to five years for the treatment of symptoms associated with menopause. The goals of long-term HRT are the prevention of osteoporosis and decrease in the risk of heart disease. The American College of Obstetricians and Gynecologists recommends that for treatment of menopausal symptoms, the lowest dosage of estrogen that provides effective relief should be used (1).

vasomotor symptoms is thought to be related to the rapidity in decline of estrogen (51). At first, flashes usually occur several times a day, and often interrupt sleep (25). Irritability, fatigue, and anxiety can result from sleep deprivation. For most patients, vasomotor symptoms are self-limiting, but for 25 to 50 percent of women, these flashes persist more than five years (77,82). Clinical trials have demonstrated that estrogen is effective in relieving these symptoms in about 95 percent of patients (19,75).

Estrogen has been found to relieve symptoms of menopause that affect the vagina, uterus, urethra, and bladder.[7] Estrogen replacement therapy can prevent the vaginal atrophy associated with menopause and maintain the normal tone of supporting ligaments and elastic tissues of the uterus and vagina (9,80,89). Vaginal atrophy may result in vaginal dryness, itching, burning, and infection. Vaginal atrophy can also result in pain with vaginal intercourse and resultant sexual dysfunction (10). Estrogen can also prevent atrophy of the bladder and urethra and the resultant painful urination, urgency, stress incontinence, frequency of urination, urination at night, and dripping after voiding (24,29,66,80).

The absence of estrogen may cause skin to become thinner, as the amount of collagen in the skin decreases (10,80). Estrogen stimulates the synthesis of collagen, and in postmenopausal women receiving estrogen, the collagen of the skin is maintained at premenopausal levels (11).

Some investigators have shown reductions in anxiety and depressed mood, and improvements in feelings of well being in women on HRT (21,56,88,89). This effect may be independent from its impact on menopausal symptoms (45).[8]

EVALUATION AND FOLLOWUP OF WOMEN TAKING HRT

Before hormonal replacement therapy is begun by a postmenopausal woman, the American College of Physicians (ACP) recommends that her physical condition should be assessed by a physician (3). The doctor should be aware of her medical history and her current health in light of contraindications to HRT. These contraindications include unexplained vaginal bleeding, acute liver disease, chronic impaired liver function, recent vascular thrombosis, breast cancer, and endometrial cancer.

The American College of Obstetricians and Gynecologists (ACOG) recommends that women taking hormonal replacement therapy be monitored every year (1). At that time breast and pelvic examinations should be performed, a Pap smear should be taken, and cholesterol level and blood pressure should be monitored. If the woman is on a regime that includes a progestin and there is no excess or prolonged bleeding, there is no need for an annual endometrial biopsy. Mammograms should be performed annually on women over the age of 50.

Endometrial biopsy is not deemed to be necessary in patients on sequential PERT because the onset of bleeding can be a useful predictor of endometrial status. Patients with proliferation and

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7 Alternatives to estrogen, such as progestogens, clonidine, or ergot alkaloids, have been used for symptomatic relief of vasomotor symptoms in women who are not candidates for estrogen replacement therapy (75,81). But none of these alternatives will prevent atrophy of the vagina (81).

8 A major difference of opinion persists as to whether estrogen therapy has any direct positive effect on mood, or whether the improved well-being reported by some women is simply due to their relief from vasomotor symptoms, and possibly due to a placebo effect (60). Some studies purport to show that a large portion of the influence of hormone replacement on affect is due to alleviation of hot flashes by hormone replacement (23). Yet other studies have demonstrated that estrogen therapy directly affects mood (12). Campbell and Whitehead, in a double-blind study of 64 women over four months, demonstrated significant improvements in certain psychological problems such as anxiety, irritability, worry about age, and optimism. They found that estrogen significantly improves anxiety and other psychological symptoms even in menopausal women who had had no vasomotor symptoms. However, a direct biological effect of loss of estrogen with menopause on depressed mood has not been demonstrated (35). Although estrogen may help alleviate depressed mood that accompanies menopause (44), major depression requires psychiatric treatment (35).

hyperplasia of the endometrium bleed earlier in the cycle than is normal with sequential PERT (59,87).

COMPLIANCE WITH HRT

A number of studies that have examined rates of compliance with HRT have in general found long-term compliance rates to be low. One study of 1,586 women enrolled in the Harvard Community Health Plan who received new prescriptions for HRT found that 27 percent stopped taking HRT within 100 days of receiving the prescription and 40 percent had stopped after one year (50).

Some studies distinguish between commencement compliance (the proportion of women prescribed HRT who initiate therapy) and maintenance compliance (proportion of women on HRT who continue to take it over a specified period of time). Speroff et al. (1991) estimated that the commencement compliance rate for women with natural menopause is between 21 and 60 percent (69). The five-year maintenance compliance rate is between 5 and 34 percent. For women with bilateral oophorectomies, the commencement compliance rate is between 31 and 89 percent. Their five-year maintenance rate is 13 to 71 percent (69).

Compliance with HRT tends to decrease over time. One study conducted for Wyeth Ayerst examined compliance with HRT in postmenopausal women who were members of a prepaid group health benefit plan and who filled prescriptions for conjugated equine estrogens (Premarin, Wyeth Ayerst) (83). Data on rates of compliance were gathered from pharmacy and medical records. Compliance rates were determined by comparing the number of days Premarin was prescribed to the number of days for which Premarin was dispensed. They found that compliance declined from 62.7 percent over one year, to 56.1 percent over three years and to 46.8 percent over seven years.

Compliance with HRT is affected by various factors, and knowledge of these factors suggests ways of improving compliance. In addition, knowledge of these factors is important in understanding how bias may affect our interpretation of observational studies of HRT's risks and benefits. (See appendices F and I for a discussion of bias.)

In general, compliance rates with drugs will be lower if the patient suffers no physical symptoms or if the symptoms disappear before the end of the treatment (62). Women who suffer from more severe menopausal symptoms, such as hot flashes, are more likely to use hormone replacement therapy. It has been found that women with surgical menopause are more likely to use and comply with long-term hormone replacement therapy, in part because their menopausal symptoms tend to be more severe (13,43). Leaner women are more likely to use hormonal replacement therapy; because body fat is an important nonovarian source of estrogen production, thin women tend to have more severe menopausal symptoms than women who are heavier (34). Women who smoke cigarettes are more likely to take HRT, possibly because of an antiestrogenic effect of smoking, which intensifies menopausal symptoms (38). But the proportion of women who use HRT for relief of acute menopausal symptoms declines in the years following menopause as these symptoms diminish in frequency and severity.

Women typically do not suffer symptoms of osteoporosis, such as hip fractures or kyphosis, until many years after menopause. Because low bone mineral density (BMD) does not have obvious symptoms unless fracture occurs, bone density measurement may increase commencement and maintenance compliance with HRT. Some experts have suggested physicians could use densitometry to help patients who are undecided about initiating HRT to "visualize" their low bone mass (57).[9] In addition, maintenance compliance might

9 Measurements of biochemical markers of bone resorption may also be used to improve compliance with HRT. These markers may allow the clinician to identify patients who are failing to respond to HRT, which may be because the patient is not complying with the prescribed regimen (41a). The use of biochemical markers of bone resorption as a tool to improve compliance with HRT has not been evaluated (Id.).

be improved by using densitometry to follow a patient's bone density over time, although there is no evidence available to test this possibility.

Women with below-normal BMD as determined by densitometry are more likely to take estrogen as a preventive measure for osteoporosis (65). One study surveyed 261 women in California who had had their BMD measured. Postmenopausal women who had below-average BMD for their age, sex, and race combination were five times as likely to begin taking estrogen as women with normal densitometry results (odds ratio 8.4, 95 percent confidence interval 3.4 to 20.9). While the study showed that more women with low BMD at densitometry initiated estrogen replacement therapy than women with normal BMD, it did not report on the effect of densitometry on long-term compliance with HRT. Another study of compliance with HRT among 352 postmenopausal women who had BMD measurements, however, found that 40 percent of the women who were recommended HRT for low bone density were not taking HRT eight months after referral (67)

Women's attitudes and beliefs about HRT affect compliance with hormonal replacement therapy. In general, compliance with drugs will be lower if the patient is not convinced the medication will help or if the patient is afraid of the development of side effects (62). Many women are resistant to taking HRT because it is "not natural" (54). Women may discontinue HRT because of unacceptable side effects, such as resumed menstruation, breast tenderness, weight gain, headaches, and abdominal bloating (55). In addition, women may decide not to use HRT because it may increase their risk of endometrial cancer and breast cancer.

Greater patient education about the magnitude and direction of effects and risks may improve compliance with HRT. In general, compliance is better with more patient education about the disease and the regimen (55).

The uptake and compliance with HRT may also be affected by physicians' beliefs and recommendations. A number of factors appear to influence physicians in their prescribing of HRT, including estimates of benefits and risks that may not be supported by scientific data (74). In addition, some physicians appear to use patterns of administration of HRT that may diminish the chance of appropriate patient compliance and fail to adjust therapy when problems occur (74).

The clinical setting may also have an impact on compliance. Experimental clinical trials of HRT have generally shown better rates of compliance than studies of HRT compliance outside of the trial setting. For example, one clinical trial of HRT in women with hysterectomies showed perfect compliance during the 18 months of the study (39). A clinical trial of estrogen patches showed perfect compliance over four months (58). Both of these clinical trials involved small samples of women (22 and 12, respectively.) In addition, compliance may be better in clinical trials because there are more intensive efforts at follow-up than generally occur in the normal clinical settings.

Compliance is also affected by the age at which hormonal replacement therapy is initiated. Elderly postmenopausal women more frequently object to the resumption of menstrual bleeding induced by PERT than perimenopausal and early postmenopausal women (6). Other factors also affect the compliance of elderly patients with medication regimens. A patient is less likely to comply if she has a poor understanding of the prescription instructions, if the therapy is long term, or if the prescription has complex instructions (62). An elderly woman may suffer from impaired vision or hearing that could impede her ability to read a drug label or hear instructions for its use. In addition, many elderly people live alone, and it has been shown that people who live alone are less likely to comply with a medication regimen than those who do not (62). In addition, the expense of certain medications may have an impact on compliance by the elderly with limited fixed incomes.

Behavioral patterns of women who take estrogen, such as regular physician visits (to refill prescriptions, for example), differentiate them from women who do not take estrogen. In order to examine the effect of health behaviors on HRT use,

TABLE E-3: Combination Estrogen/Progestin Products for Osteoporosis in the U.S.

Generic name	Brand name (t.m.)	Manufacturer	FDA-approved indications	Recommended dosages for osteoporosis and menopausal symptoms
Conjugated estrogens and medroxyprogesterone acetate for continuous HRT	Prempro	Wyeth-Ayerst	1) Moderate to severe vasomotor symptoms of menopause 2) Vulvar and vaginal atrophy 3) Osteoporosis (in women with an intact uterus)	Menopausal symptoms. 0.625 mg CEE and 2.5 mg medroxyprogesterone acetate daily Osteoporosis: 0.625 mg CEE and 2.5 mg medroxyprogesterone acetate daily
Conjugated estrogens and medroxyprogesterone acetate for sequential HRT	Premphase	Wyeth-Ayerst	1) Moderate to severe vasomotor symptoms of menopause 2) Vulvar or vaginal atrophy 3) Osteoporosis (in women with an intact uterus)	Menopausal symptoms. 0.625 mg CEE (cyclic administration) and 5 mg medroxyprogesterone acetate for last two weeks of cycle Osteoporosis: 0.625 mg CEE (cyclic administration) and 5 mg medroxyprogesterone acetate for last two weeks of cycle

KEY: CEE = conjugated equine estrogen, HRT = hormone replacement therapy, t m = trademark

SOURCE: Office of Technology Assessment, 1995

Barrett-Connor et al. studied 1,057 postmenopausal women from the same socioeconomically upper-middle-class community in California who participated in a clinic evaluation of their estrogen use patterns (8). After an average of 4.4 years later, 95 percent of these women completed a mailed health survey questionnaire. This questionnaire asked them about recent changes in lifestyle behaviors that affect their health, such as consumption of dietary fat, salt use, and exercise habits, as well as frequency of blood pressure checkups, mammograms, and Pap smears.

The study found that women who were currently using HRT were significantly more likely to have recently implemented new healthy lifestyle behaviors than women who had never used HRT (8). For example, 70 percent of the women who were currently using HRT had had a mammogram in the last year, whereas only 45 percent of the women who had never used HRT had had one. Thirty-eight percent of current users had increased their daily exercise over the past year, whereas only 29 percent of never users had increased their exercise. Women who never used HRT were less likely to have implemented healthy behavior changes, and were least likely to have had screening evaluations than women who had used HRT.

Compliance may be affected by the type of packaging. One study of 177 patients compared a calendar-oriented system of HRT packaging to conventional packaging of HRT (50). Compliance rose from 23 percent when the pills were provided in conventional packaging to 82 percent when the pills were provided in a prepackaged blister card system. Wyeth-Ayerst introduced a prepackaged blister card system of packaging in 1995. (See table E-3.)

Thus, a variety of factors affect compliance with HRT. Increased awareness of the factors affecting compliance with HRT suggests ways of improving long-term compliance.

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Appendix F: Evidence on Breast Cancer and Hormonal Replacement Therapy

F

Breast cancer, after lung cancer, is the second leading cause of death from cancer. The American Cancer Society estimates that one in nine American women will develop breast cancer during her lifetime (65). The impact of hormone replacement therapy (HRT) on the risk of breast cancer, even if small, would be substantial given the high baseline risk, as well as the societal cost, of this illness. For this reason, this question has been one of the most widely studied with modern epidemiologic techniques. Unfortunately, given the complexity of the issues involved, no clear-cut answer is available at this time.

This appendix reviews the evidence linking HRT to an increase in the risk of breast cancer. First, the biological plausibility of a link between HRT and breast cancer risk will be reviewed. Second, the epidemiological evidence of HRT and breast cancer risk will be reviewed. Virtually all of the epidemiological evidence is observational, consisting of case-control studies and cohort studies. The findings, and discussion of the strengths and weaknesses of the studies on which they are based, follow.

BIOLOGICAL PLAUSIBILITY

The relationship of HRT and breast cancer is consistent with a number of observations. Bittner first suggested that estrogen could increase the incidence of breast cancer, by examining the role of estrogens in the development of mammary tumors in mice (3). Subsequently, Moolgivkar and Knudson proposed that estrogen could increase the risk of breast cancer by increasing the rates of division and numbers of breast cells, which increases the likelihood that an initiating factor (such as ionizing radiation, chemicals, or viruses) will damage cellular DNA (51). Such DNA damage, in turn, leads to a series of errors in cell division, producing so-called "intermediate" cells, which finally results in transformed, or malignant cells.

The hypothesis that HRT increases breast cancer risk is further supported by observations that factors that increase a woman's exposure to estrogen and progestin increase her risk of breast cancer. Thus, early menarche (age of onset of menstruation) and late menopause are associated with an increased breast cancer risk (75). Also, women who have had surgical removal of the ovaries have a lower breast cancer risk (77). There is also strong evidence that obese postmenopausal women are at an increased risk of breast cancer (19). This may be because the chief source of estrogen after menopause is the conversion in fat tissue of the hormone androstenedione, made in the adrenal gland, to the estrogen estrone (46).

It is uncertain whether the addition of progestins would increase the risk of breast cancer above estrogen alone. Key and Pike have reviewed the experimental evidence bearing on the hormonal control of breast cell division (42). They noted that breast cell division peaks during the later phase of the menstrual cycle, corresponding to a progesterone peak. They concluded that, although knowledge of the hormonal control of division rates was incomplete, the available data could support two possible interpretations.

The first model suggests that women receiving a combination of estrogen and progestin will have an increased risk of developing breast cancer over those receiving estrogen alone. This "estrogen plus progesterone" model posits that estradiol, the major ovarian estrogen, itself may induce breast cell division in the early phase of the menstrual cycle. However, the addition of progesterone, produced in the later phase of the menstrual cycle, induces much more cell division, perhaps because estrogen produced in the early phase of the menstrual cycle has stimulated the formation of progesterone receptors on breast cells (42). This increased cellular proliferation then places the breast tissue at risk for malignant change.

The alternative model suggests that the addition of a progestin will have little effect on the risk of breast cancer associated with estrogen. This "estrogen alone" hypothesis is supported by experimental data demonstrating that progesterone shows little significant cell division-stimulating effect. These results suggest that cell division is induced by estradiol alone, with little contribution by progesterone (42). Such an explanation, the authors note, requires a dose-response relationship between the plasma concentration of estradiol, which peaks at the end of the early phase of the menstrual cycle, and the amount of breast cell division. Furthermore, such a model must account for the 4-to 5-day lag between these changes in estradiol concentration and the subsequent changes in rates of cell division observed in breast tissue.

CASE-CONTROL STUDIES

Tables F-1 and F-2 at the end of this appendix present the results of 30 case-control studies of the risk of breast cancer in users of hormonal replacement therapy. The fourth column of the table compares the risk of breast cancer among never users of hormonal replacement therapy with those who have ever used hormonal replacement therapy. Of these 30 case-control studies, five showed an increased risk of breast cancer among ever users (30,33,37,44,83). Nineteen studies demonstrated no increased risk of breast cancer in ever users of hormonal replacement therapy. However, most of these latter studies found increased risks among certain subgroups of users. The other 6 studies either did not compare ever users to never users (2,23,35) or did not provide statistical analysis of results (19,48,60).

Duration

The fifth column of tables F-1 and F-2 describe the relationship of breast cancer risk to duration of estrogen use. Most of the studies finding no increase in the risk of breast cancer among ever users also found no correlation of breast cancer risk with duration of use. However, several studies, including most studies which have found the risk of breast cancer to increase among ever users have found that the risk of breast cancer increases with longer durations of use (2,6,18,23,27,28,44,63, 84). In addition, two studies found increased risks among users with the greatest cumulative dose, which is based on average daily dose multiplied by the duration of use (63,82). However, Jick found an increased risk among ever users, but did not find a correlation with duration of use (80). Three studies found increased risk only among women with shorter durations of use (33,35,53). In these studies, increased risk of breast cancer among the groups of users of the longest duration may have been difficult to detect because of the relatively smaller number of women in these groups.

Dose

The sixth column of tables F-1 and F-2 describe the relationship of breast cancer to the dose of estrogen. Bergkvist found a significantly increased risk of breast cancer among users of the potent estrogen diethylstilbesterol and among users of "other" estrogens, which included users of relatively high dose injectable forms of estrogen (2). However, the study found no correlation of risk with the doses of oral conjugated estrogens (CE) that are commonly used in hormonal replacement therapy (2). Hoover found a trend toward increased risk among users of high doses of estrogens (greater than 1.25 mg CE per day or the equivalent) (28). Hulka found an increased risk of breast cancer among users of injectable estrogens, but no significant increased risk among users of the highest doses of oral estrogens (greater than 1.25 mg CE per day or the equivalent) (33). Four studies found no correlation between risk of breast cancer and dose of estrogen (37,39,40,49).

Recency

The sixth column of tables F-1 and F-2 describe the relationship of the recency of estrogen use, or the time since last use of estrogen, to the risk of breast cancer. Thirteen case-control studies have examined this issue. Of those, seven found no relationship between recency of estrogen use and breast cancer risk. Hulka found an increased risk of breast cancer among users whose last dose was two to five years past, but no increase in risk among users whose last dose was within the past year or among those whose last dose was six or more years ago (33). Kaufman found a reduced risk of breast cancer among women with a surgical menopause whose last dose was 10 or more years ago (39). The author explains that this low relative risk may be due either to chance or the fact that women who have had their ovaries removed and are more likely to be prescribed estrogen generally for a short period of time also have a lower risk of breast cancer (39). La Vecchia found a significantly increased risk of breast cancer among users of estrogens whose last dose was 10 or more years ago, but this risk was only marginally significant when adjusted for a number of confounding factors (44). Nomura found a significantly increased risk of breast cancer among women of Japanese ancestry whose last dose was eight or more years ago when compared with community controls but not when compared with hospital controls (53). No correlation of risk with recency of use was found among white women (53).

Time Since First Use

The sixth column of tables F-1 and F-2 present data on the relationship of breast cancer to the time since first use of HRT, or latency. Eleven of the case control studies address this issue. Eight of the case control studies show no correlation of risk with time of first HRT use. Ewertz found an increased risk among women with natural menopause more than five years prior to breast cancer diagnosis, and whose first dose of hormonal replacement therapy was more that 12 years ago. No similar increase in risk was found in women with natural menopause within five years of breast cancer diagnosis or women with surgical menopause (18). Hulka found an increased risk among women whose first dose of hormonal replacement therapy was five to nine years ago, but no significant increase in risk was detected in users whose first dose was 10 or more years ago (33). Weinstein found on increased risk of breast cancer only in women 10 to 19 years since first use (80).

COHORT STUDIES

Cohort studies of the relationship of breast cancer to use of hormonal replacement therapy are presented in tables F-3 and F-4 at the end of this appendix. Of the 18 studies identified by OTA, seven demonstrated a statistically significant increased risk of breast cancer among users of hormonal replacement therapy. Six studies did not show an increased risk of breast cancer that was statistically significant. One study found a decreased risk of breast cancer among users of hormonal replacement therapy (78). Three studies provided no statistical analysis of results. One study demonstrated a decreased risk of breast cancer among users of estrogen with progesterone,

but this study did not control for confounding variables (20). A decreased risk of breast cancer among users of estrogen and progesterone was also found in the only clinical trial to examine this issue (52) (described below); however, a lower risk of breast cancer in users of estrogen and progesterone has not been confirmed by other studies (2,67).

Duration

Tables F-3 and F-4 also show the effect of the duration of use of hormonal replacement therapy on breast cancer risk. Some studies were able to demonstrate an increase in risk of breast cancer with increasing duration of use (2,29,61). However, five studies were not able to detect an increase in risk with increased duration of use. Colditz found an increased risk among current users of five to 10 years, but not among users of shorter or longer durations (13). Schairer found an increased risk only of preinvasive *(in situ)* cancers with duration of ERT use (67).

Dose

The few cohort studies that have looked at the relationship of dose to risk of breast cancer have not consistently demonstrated an increased risk with increasing dose of estrogen (13,29,61).

Recency and Time Since First Use

Some studies have demonstrated an increased risk with current users of estrogen, but not with past users (13, 14,89). Other studies have found that the risk of breast cancer increases with time since first use (34,35).

CLINICAL TRIALS

Only one clinical trial has examined the relationship of hormonal replacement therapy to breast cancer risk (52). Subjects were continuously hospitalized postmenopausal women. Treated women and control group members were matched for age, smoking history, and medical diagnosis. The treatment group received estrogen-progestin hormone replacement therapy. The control group received placebo. Double-blinded randomization was discontinued after 10 years. In the subsequent 12 years, women were offered the choice of starting, stopping, or continuing hormone replacement therapy. During the 10-year clinical trial, there were no significant differences in breast cancer incidence between the treated and the placebo group. After 22 years of follow-up, there was a statistically significant increase in breast cancer risk in never users of hormonal replacement therapy versus ever users. However, the size of this study was quite small, involving 89 pairs of women, and the results are unstable.

COMBINED ESTROGEN-PROGESTIN THERAPY AND BREAST CANCER RISK

It is uncertain whether the addition of progestins to estrogen replacement therapy would alter HRT users risk of breast cancer, as few studies have examined this issue. Bergkvist and colleagues examined this issue in a study of breast cancer in a cohort of 23,000 women from the Uppsala Health Care Region of Sweden. They found a significant increase of breast cancer in users of estrogen alone; they also found a similar increase in risk of breast cancer among users of combined estrogen and progestin. The increase in risk among combined estrogen-progestin users, however, did not reach statistical significance, in part due to the relatively small number of users of combined estrogen-progestin in the cohort. The investigators concluded that progestins offered no protection against the development of breast cancer (2).

A recent cohort study by Schairer and colleagues found- that users of estrogen-progestin combinations may have a higher risk of breast cancer than users of estrogen alone (67). The study examined the incidence of breast cancer among 49,017 postmenopausal women who had participated in the Breast Cancer Detection Demonstration Project (BCDDP). For ever users of estrogen alone, there was no increased risk of breast cancer. For users of estrogen and progestin combinations, however, there was an increased risk of breast cancer that was of marginal statistical significance

(relative risk 1.2 (95 percent confidence interval 1.0 to 1.6)).

All of the studies of hormone replacement and breast cancer risk, except one, are observational, so the possible impact of selection bias cannot be entirely ruled out. Barrett-Connor explained that it is uncertain how selection bias may affect the results of studies of HRT use and breast cancer (1 a). Some biases may result in an exaggerated estimate of breast cancer risk in HRT users. For example, women who take hormonal replacement therapy tend to be more educated and of higher socioeconomic status than other women (la). Studies have shown that women of higher socioeconomic class are at higher risk of breast cancer. Therefore, epidemiological studies that fail to account for differences in socioeconomic status between HRT users and nonusers may overestimate the risk of breast cancer in HRT users.

Women on HRT have been found to be more likely to have mammograms (2a). Breast tumors in HRT users are therefore more likely to be detected. This bias may explain for the lower stage and grade of tumors detected in HRT users, and the improved prognosis of breast cancers in HRT users (la,9). (See discussion below.)

Other biases may result in an underestimate of breast cancer risk in HRT users (la). Women who have an early menopause or surgical removal of the ovaries (oophorectomy) are more likely to be treated by their physicians with HRT. Breast cancer risk in these women may be underestimated because both early menopause and oophorectomy are associated with decreased risks of breast cancer. Women are more likely to be prescribed estrogen if they have menopausal symptoms, and thin women tend to have more severe menopausal symptoms. Thin women are also at decreased risk of breast cancer, so this is another source of bias.

Physicians may be reluctant to prescribe HRT to women with benign breast disease or a family history of breast cancer, another source of decreased estimate of risk (la). And some physicians will not prescribe HRT until their patient has had a mammogram, and if the mammogram is abnormal, will not prescribe HRT.

Women who take hormonal replacement therapy are more likely to engage in other healthy behaviors. And women who are willing to take hormonal replacement therapy long-term are, by definition, more compliant. As has been discussed in detail in Appendix I, compliant women are less likely to get heart disease, cancers, and other diseases. Although epidemiological studies have attempted to statistically control for many of these sources of bias, it has not been possible to completely control for so-called compliance bias because of its ill-defined nature.

The uncertainty about the relation between breast cancer risk and hormone replacement therapy will not be resolved until we have the results of a randomized clinical trial of HRT in postmenopausal women (32). Because the increase in risk of breast cancer in HRT users appears to be small, a large study would be required to have sufficient statistical power to detect this small increase in risk. Given that the risk of breast cancer increases with duration of use, the controlled clinical trial would take 10 or more years to complete.

The Women's Health Initiative, sponsored by the National Institutes of Health, is a large long-term randomized clinical trial examining the effect of hormone replacement therapy on heart disease and osteoporosis in postmenopausal women. (See description in Appendix I.) This trial will also help to resolve many of the questions about the relationship between hormone replacement therapy and breast cancer risk and other diseases affected by hormone replacement therapy.

Problems with conducting such a study arc the expense of the trial and the practical problems in conducting a clinical trial long-term. Also, because sequential and continuous hormonal replacement therapy causes bleeding and other symptoms, both the investigator and the subject will become aware of their assignment, introducing a source of bias. Finally, by the time the trial is completed, new HRT regimens may be available, raising the question of whether the results of the Women's Health Initiative apply to these new regimens.

STAGE OF BREAST CANCER AT DIAGNOSIS IN HRT USERS VERSUS NONUSERS

There is some evidence that estrogen users develop breast cancer of lower stage and grade than breast cancers in nonusers. This maybe an artifact of surveillance bias or may be because estrogen induces a less malignant form of breast cancer. In a population-based case control study of breast cancer in postmenopausal women, Brinton and colleagues found that there was a significant trend of greater risk of breast cancer with increased duration of HRT use, and that this increase in risk was greatest for the lowest stage tumors (6). After 10 or more years of estrogen use, the increase in risk of large (greater than 1 cm) invasive breast cancers was 1.29 (p less than 0.05), but the increase in risk of small (1 cm or less) tumors and carcinoma in situ was 1.51 (p less than 0.05) and 1.90 (p less than 0.05), respectively.

Hunt and colleagues, in a study of a cohort of 4544 British women receiving HRT at menopause clinics, found that, of the 40 breast cancers that developed among the cohort that were identified by stage, 27 (68 percent) were classified as Stage I (nonmetastatic tumors 2 cm or less) at diagnosis, which is a higher proportion of early stage tumors at diagnosis than expected based on comparison with stage at breast cancer diagnosis in the general population (34). The lower than expected stage of breast cancer at diagnosis in cohort members, however, could be explained by the fact that 1) the average member of the cohort had been followed for less than 5 years, and 2) cohort members, all of whom were on HRT at recruitment, presumably did not have any previous diagnosis of breast cancer at that time (57).[10]

Squiteri and colleagues found that hormone users present with slower growing breast tumors of earlier stage than nonusers, possibly resulting in improved prognosis (70). Breast cancers from 35 women who had taken HRT (mostly estrogen and progestin combinations) were compared to breast cancers from postmenopausal women who had never taken hormones, matched for age and type of breast cancer to HRT users. They found that HRT users had smaller tumors, significantly less spread to lymph nodes, and had significantly lower S-phase fractions (a measure of the rate of cancer cell division). The investigators concluded that the small tumor size, low S-phases, and limited nodal involvement of HRT users suggests that, despite a possibly increased risk of breast cancer, the mortality rate for breast cancer in HRT users will not be increased in comparison with nonusers. The investigators could not rule out the possibility, however, that the results may have been due to better surveillance and earlier diagnosis of breast cancer in HRT users.

Bonnier and colleagues concluded that the lower stage of breast cancers in HRT users was not due to surveillance bias (4). The investigators compared 68 postmenopausal women who were receiving HRT at the time of diagnosis of breast cancer with 282 breast cancer patients who had not received prior HRT, and whose date and age of onset of breast cancer were similar to that of the breast cancer patients that had received HRT. Patients who developed breast cancer during HRT had fewer locally advanced cancers (tumors that had extended into lymph nodes) and more well-differentiated cancers. In addition, the probability of metastasis-free survival tended to be better in HRT users. The investigators found that the favorable prognosis in HRT users was not likely to be due to better cancer surveillance among HRT users, because x-ray detection was not more frequent among patients undergoing HRT. In addition, the delay between first symptoms and

[1] Hunt and colleagues also found that short term users of HRT had a significantly lower death rate from breast cancer than would be expected by comparison with population age-specific breast cancer death rates (observed to expected ratio = 0.55 (0.28-0.96)) (34). As Pike and colleagues explained, however, for a member of the cohort to die during the five year follow up, she had to first be diagnosed with breast cancer and then die of that disease (57). The expected number of such deaths cannot be derived straightforwardly from population age-specific death rates.

diagnosis was slightly but not significantly shorter in HRT users.

Additional information is needed on whether the addition of progestin has an impact on the stage and grade of breast cancer related to estrogen. Schairer and colleagues, reporting on the results from the BCDDP cohort (described above) found that estrogen-progestin combinations were related to a larger risk of preinvasive (in situ) cancers (relative risk 2.3 (95 percent confidence interval 1.3 to 3.9)) than estrogen alone (relative risk 2.3 (95 percent confidence interval 1.3 to 3.9)), but neither estrogen or estrogen-progestin combinations were related to an increased risk of invasive cancers (67).

Jones and colleagues found evidence that tumors induced by estrogen-progestin combinations may have a better prognosis than tumors induced by estrogen alone (38). The investigators identified 460 perimenopausal and postmenopausal breast cancer patients hospitalized in Perth, Western Australia, between January 1990 and December 1991. They questioned each of the patients about HRT use, and reviewed medical records and pathology reports for data related to breast cancer prognosis. They found that the mean level of estrogen and progestin receptors was lowest in users of estrogen alone highest in users of estrogen-progestin combinations, consistent with a better prognosis for estrogen-progestin users. Levels of Cathepsin D, which is inversely related to breast cancer risk, were highest in users of estrogen alone, and lowest in nonusers. The tumors were smallest in estrogen-progestin users, and largest in users of estrogen alone, although the difference was not statistically significant. There was no significant difference in lymph node involvement of cancer between estrogen-progestin users and users of estrogen alone. The percentage of all HRT users with involved lymph nodes (23 percent), however, was significantly lower than the percentage of nonusers (44 percent). The authors stated that they could not rule out that this last finding could have been due to differences in surveillance.

BREAST CANCER MORTALITY IN HRT USERS VERSUS NONUSERS

There is conflicting evidence about whether an increased incidence of breast cancer among HRT users results in an increased rate of breast cancer deaths. A number of studies have found that estrogen users do not have an increase in deaths from breast cancer. Petitti and colleagues analyzed the 26 breast cancer deaths that occurred during 13 years followup of the 6,093 women in the Walnut Creek cohort (56). The relative risk of death from breast cancer for women who used HRT but not oral contraceptives was 0.8 (0.4 to 1.8) compared to women who used neither HRT nor oral contraceptives.

Vakil and colleagues also found reduced breast cancer mortality among postmenopausal estrogen users in a cohort of 1,483 postmenopausal women from Ontario and Saskatchewan (78). The ratio of observed to expected mortality from breast cancer among HRT users was 0.48 (p less than 0.01) for the Ontario women and 0.45 (p less than 0.01) for the Saskatchewan women.

In a cohort study of 8,881 postmenopausal residents of Leisure World Retirement Community in Los Angeles, Henderson and colleagues found a reduction in breast cancer mortality among estrogen users of 0.81 (no confidence interval provided) (26). Although the investigators did not have information about breast cancer stage at diagnosis, they suggested that estrogen users may have less extensive cancers at diagnosis than nonusers because of increased breast cancer surveillance among estrogen users and better health awareness of women who use estrogens.

Bergkvist and colleagues, in an analysis of survival rates in women with breast cancer in the Uppsala Health Care Region of Sweden, found that ever users of HRT had significantly greater survival rates than never users (2). The investigators compared survival rates in 261 breast cancer patients who used HRT prior to diagnosis with 6,617 breast cancer patients from the same geo-

graphic region who did not have any recorded use of HRT.

Information on estrogen use was obtained from a regional prescription database and from a mailed questionnaire, and information on breast cancer survival was obtained from the Swedish National Cancer Registry (2). (The registry did not, however, have information about tumor stage and grade.)

The investigators found that the relative 8 year survival rate of women diagnosed with breast cancer who used hormonal replacement therapy was 10 percent higher than those who had not taken hormonal replacement therapy, which corresponded to a 40 percent reduction in excess mortality (2). Separate analysis of relative survival by age at diagnosis showed a significant survival advantage for estrogen-treated women at each age over 50, and was greatest for estrogen-treated women 60 years old and older at diagnosis, with an approximately 40 percent lower mortality rate than never users with breast cancer.

The relative survival rates were highest for women who were current users of HRT at diagnosis, and the survival advantage of estrogen users was decreased with longer time between cessation of estrogen and diagnosis, so that the survival rates of estrogen users who had stopped taking estrogens more than 12 months before diagnosis was close to that of never users of estrogens (l). Also, the relative survival rates were best among women treated with progestins combined withestrogen during part or all of the course of HRT.

There were several possible alternative explanations of these results. First, a favorable impact of estrogens on forces of mortality other than breast cancer, most notably heart disease, may have accounted for the favorable survival rates of HRT users. Second, women who are prescribed HRT represent a healthy selection of the general population. Third, the favorable survival rates of HRT users maybe due to surveillance bias (2).

A subsequent study of breast cancer mortality by the same group attempted to correct for the "healthy user" effect (85). Despite these corrections, the investigators found no increase in breast cancer mortality, either overall or in subgroups, despite increased incidence.

Results of a study by Strickland and colleagues suggest that the favorable survival of breast cancer patients who used HRT is due to surveillance bias (73). The investigators compared the survival time between diagnosis and death of 256 postmenopausal women with breast cancer, 174 of whom were never users of estrogens, 21 of whom were past users of estrogens, and 61 of whom were currently using estrogens at the time of diagnosis. Information on survival time, as well as stage of breast cancer at diagnosis, was obtained from the Southwestern Oncology Group Tumor registry. They found that the median time between breast cancer diagnosis and death was less than 84 months for never users and past users of estrogens, and was 143 months for current users of estrogens. After controlling for stage of breast cancer at diagnosis, however, the survival time for never users and past users of HRT was not significantly different from current users.

CONCLUSIONS

Although the evidence on the link between estrogen therapy and the risk of breast cancer is based almost entirely on case-control and cohort studies, which cannot entirely control for biases and confounding factors (64), the inconsistency in results among both kinds of studies suggests that the effect of estrogens on breast cancer is likely to be small. Indeed, when they were found, such associations were generally weak. Discrepancies in the results among studies are not readily explained by study design or implementation and may likely be due to chance.

For purposes of this model, we assumed in the base case that the relative risk of breast cancer with HRT would be a modest 1.35 times the baseline rate in the population of women of a certain age, but the higher risk would not occur until the duration of use had exceeded 9 years. This increase in risk is consistent with the range of estimates of breast cancer risk with long-term use

from several recent metaanalyses and epidemiological reviews (Grady (relative risk 1.25 (95 percent confidence interval 1.04 to 1.51) for eight or more years of ERT use) (21); Steinberg (relative risk 1.3 (1.2 to 1.6 after 15 years of use) (72); Colditz (relative risk 1.23 (95 percent confidence interval 1.08 to 1.40) for 10 or more years of estrogen use) (12); Sillero-Arenas (relative risk 1.23 (1.07 to 1.42) after more than 12 years use) (69); Hulka (relative risk approximately 1.3 to 1.5 with long-term use) (31); Steinberg (relative risk 1.15 to 1.29 after 10 years of CEE use) (71); Mack (relative risk 1.2 at 5 years of use, increasing to 1.4 at 10 years of use) (47); Prentice (relative risk 1.3 for ever use, and possibly larger risks with long-term use) (59).

Once duration exceeds nine years, the relative risk of breast cancer is assumed to remain elevated for the rest of the woman's lifetime. This assumption is consistent with the observation that breast cancer risk remains elevated in women with late menopause and the hypothesis by Pike that HRT induces a hormonal milieu similar to late menopause (57,58).

Because of the great uncertainty about the magnitude and exposure pattern of risk elevation, the best case assumption was that there would be no increased risk of breast cancer among users of HRT. This estimate is consistent with the metaanalysis by Dupont and Page (16), who limited their analyses to studies of conjugated estrogens, and excluded European studies where use of stronger synthetic estrogens is common. This estimate is also consistent with the metaanalyses of Khoo and Chick (43) (no increase in breast cancer risk), Henrich, (24) (no increased risk of breast cancer among ever-users of estrogens) and Armstrong (summary relative risk 0.96 (0.89 to 1.05) after adjustment for menopausal status; no effect of duration of use) (l).

Under the worst case, we assumed a relative risk of 2.0 after 9 years of therapy. This worst-case estimate is consistent with the largest relative risks of breast cancer found in cohort studies of HRT users (2,35,50,76); these large increases in risk were generally associated with long-term use. This estimate is also within the range of estimates from epidemiological reviews by Persson and colleagues (relative risk 1.5 to 3.0 with 10 to 15 years of use) (55), Pike (relative risk 1.75 after 20 years of ERT use) (57) and Henderson and colleagues (relative risk 1.5 to 2.0 if moderate doses of CEE are used for 10 to 20 years) (26). We have also assumed that there was no difference in stage distribution or mortality from breast cancer in estrogen users. Observational studies that have found better stage and grade breast cancers in HRT users have inherent risks of surveillance bias.

Finally, we have assumed that, once diagnosed with breast cancer, women would be taken off HRT. There is, however, a debate in the literature over whether women previously treated for breast cancer may start or resume HRT (11, 15,36,45,74). Proponents argue that there is little direct evidence that HRT has an adverse effect on women previously treated for breast cancer who subsequently received HRT (81). The National Cancer Institute recently announced the initiation of a randomized clinical trial to determine the influence, if any, of HRT on the clinical course of breast cancer (79).

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TABLE F-1: HRT and Breast Cancer Risk (Hospital-Based Case-Control Studies) (Page 1 of 10)

Author	Description of cases and controls	Number of oases and controls	Relationship of breast canoer to estrogen use [a,b]	Relationship of breast cancer to duration of estrogen use [a,b]	Relationship of breast cancer to dose, recency, and latency of estrogen use [a,b]
Boston Collaborative Drug Surveillance Program (1974)	Cases and controls were consecutive postmenopausal patients, ages 45 to 64 years, admitted to the general medicine and surgical wards of 24 hospitals in the Greater Boston area in 1972. Cases had surgically confirmed breast cancer. Controls were postmenopausal women who were admitted to these hospitals with acute illnesses, elective surgery, or orthopedic treatment. Patients were interviewed during admission.	51 breast cancer cases; 774 controls	9% of cases were estrogen users; 8% of controls were estrogen users; the difference was not statistically significant	"Duration of use in the cases of breast cancer . . was similar to that of control users."	
Sartwell (1977)	Cases were women 20 to 74 years of age with carcinoma of the breast admitted to Johns Hopkins Hospital between 1969 and 1972. Controls were chosen from among other patients except those from the obstetric or gynecology services. All subjects were given a questionnaire by an interviewer.	284 cases (65,8% post menopausal) (1 9.7% noncontraceptive estrogen users); 367 controls (76.8% postmenopausal) (26.7% noncontraceptive estrogen users)	Adjusted RR: 0.82 (0.6-1 .2)* ● adjusted for age, race, marital status, menopausal history, and pregnancy history.	<6 mo.: 0.87 6-11 mo.: 0.61 1-1.9 yrs.: 1.40 2-4.9 yrs.: 0.70 >5 yrs.: 0.62 None of the adjusted relative risks were significantly different from unity.	
Wynder (1 978)	Cases were pre- and postmenopausal white women selected from seven hospitals in New York City, with diagnosis of breast cancer between 1969 and 1975. Controls were white women admitted to the surgical services of these same hospitals during the same period. All subjects were interviewed.	785 cases (267 postmenopausal); 2,231 controls (630 postmenopausal)	34.1 % of postmenopausal cases and 36.8% of postmenopausal controls used estrogen (nonsignificant difference).		

TABLE F-1: HRT and Breast Cancer Risk (Hospital-Based Case-Control Studies) (Page 2 of 10)

Author	Description of cases and controls	Number of cases and controls	Relationship of breast cancer to estrogen use[b]	Relationship of breast cancer to duration of estrogen use [a,b]	Relationship of breast cancer to dose, recency, and latency of estrogen use [a,b]
Ravnihar (1979)	Cases and controls were women ages 15 to 64 years selected from patients admitted to a Slovenian hospital. Cases were women admitted for aspiration or biopsy of malignant or benign breast diseases. Two controls from other hospital services were selected for each case and matched for age and date of admission. Interviews were conducted between 1972 and 1974.	374 breast cancer cases (184 were ages 50 to 64), 748 breast cancer controls (368 were ages 50 to 64)	Ages 50-64. cases 11.4% controls 11.7% No tests of statistical significance were performed.	Ages 50 to 64: <24 mo.: 11/1 84 breast cancer cases 30/368 controls >24 mo.: 3/1 84 breast cancer cases 8/368 controls unknown duration 7 cases, 5 controls	Current users (ages 50 to 64). 1/1 84 breast cancer cases 5/368 controls Past use: 20/1 84 breast cancer cases 38/368 controls
Jick (1980)	Cases were postmenopausal women, ages 45 to 64, identified from a prepaid health care organization's (Group Health Cooperative of Puget Sound) records as having the diagnosis of breast cancer between 1975 and 1978. Controls were postmenopausal women ages 45 to 64 years matched for age with cases and hospitalized about the same time. Information on cases and controls was obtained from interviews and medical and pharmacy records.	97cases (39% current estrogen users); 139 controls (37% current users)	Natural menopause: 3.4 (90% 2.1 -5.6) for current users (last use within 12 months of date of diagnosis) versus nonusers, Hysterectomized women. 1,1 (90% 0.7-1 .9)	Duration had no effect on risk of breast cancer.	Dose had no effect on risk of breast cancer.

TABLE F-1: HRT and Breast Cancer Risk (Hospital-Based Case-Control Studies) (Page 3 of 10)

Author	Description of cases and controls	Number of cases and controls	Relationship of breast cancer to estrogen use [a,b]	Relationship of breast cancer to duration of estrogen use [a,b]	Relationship of breast cancer to dose, recency, and latency of estrogen use [a,b]
Kelsey (1 981)	Cases were women ages 45 to 74 years admitted to Connecticut hospitals between 1977 and 1979 with newly diagnosed breast cancer. Controls were women of the same age span admitted to other surgical services (excluding gynecology) between 1977 and 1979. All cases and controls were interviewed.	330 cases (9% users); 1,348 controls (10% users)	One or both ovaries intact (pre- and postmenopausal). O.R. 0.9 (0.6-1 .2) Both ovaries removed: O.R. 0.9 (0.5-1 .5)	At least one ovary intact (pre- and postmenopausal). 1-49 mg - months. O.R. 0.9 (no c.i.) >50 mg - months: O.R. 0.6 (test for trend: p= 0.08) Both ovaries removed: 1-49 mg - months: O.R. 0.7 (no c.i.) >50 mg - months: O.R. 1.0 (test for trend: P= O.88) "For estrogen-replacement therapy, there is a nonsignificant decrease of less than 5 percent in risk for breast cancer with each year of use. "	

TABLE F-1: HRT and Breast Cancer Risk (Hospital-Based Case-Control Studies) (Page 4 of 10)

Author	Description of cases and controls	Number of cases and controls	Relationship of breast cancer to estrogen use [a,b]	Relationship of breast cancer to duration of estrogen use [a,b]	Relationship of breast cancer to dose, recency, and latency of estrogen use [a,b]
Hulka (1 982)	Cases were postmenopausal women admitted to two North Carolina hospitals between 1977 and 1978 with a diagnosis of breast cancer. Hospital controls were postmenopausal women admitted to these same hospitals with problems that were not gynecologic or referable to the breasts. Controls were matched to cases by age, race, date of admission, and hospital. Postmenopausal community controls were obtained from hospital referral regions. All study subjects were interviewed.	163 cases (52 users), 372 hospital controls (90 users), 737 community controls (171 users)	Estrogen use was defined as use greater than 6 months. Ever use: natural menopause 1.8 ($p < 0.05$) (comm. controls); 1.7 ($p < 0.05$) (hosp. controls) Ever use (oral estrogens only, excluding users of injectable estrogens): 1.3 (NS) (comm. controls); 1.2 (NS) (hosp. controls) Surgical menopause. 1.3 (NS) (comm. controls); 1.2 (NS) (hosp. controls)	Natural menopause. 0,5-3 yrs.: 2.1 ($p < 0.05$) (comm. controls); 2.6 ($p < 0.05$) (hosp. controls) 4-9 yrs. :1.5 (NS) (comm. controls); 1.6 (NS) (hosp. controls) 10+ yrs.: 1.7 (NS) (comm. controls); 0.7 (NS) (hosp. controls)	Natural menopause. <0,625 mg conjugated estrogen (or equivalent). 1.9 (NS) (comm. controls), 1.8 (NS) (hosp. controls) >0,625 mg: 1,0 (NS) (comm. controls), 0.8 (NS) (hosp. controls) Injectable, 4,4 ($p < 0.05$) (comm. controls) 4.0 ($p < 0.05$) (hosp. controls) Recency (time since last use): Natural menopause. O-1 yr.: 1.6 (NS) (comm.); 1,3 (NS) (hosp.) 2-5 yrs., 2,2 (NS) (comm.), 3.2 ($p < 0.05$) (hosp.) 6+ yrs.: 1.8 (NS) (comm.); 1.8 (NS) (hosp.) Latency (time since first use): Natural menopause: 0.5-4 yrs.: 1.2 (NS) (comm.); 1,7 (NS) (hosp.) 5-9 yrs.: 2.4 ($p < 0.05$) (comm.), 3.1 ($p< 0.05$) (hosp.) 10-14 yrs.: 2.1 (NS) (comm.): 1.3 (NS) (hosp.) 15+ yrs.: 1,5 (NS) (comm.); 1.4 (NS) (hosp.)

TABLE F-1: HRT and Breast Cancer Risk (Hospital-Based Case-Control Studies) (Page 5 of 10)

Author	Description of cases and controls	Number of cases and controls	Relationship of breast cancer to estrogen use [a,b]	Relationship of breast cancer to duration of estrogen use [a,b]	Relationship of breast cancer to dose, recency, and latency of estrogen use [a,b]
Sherman (1983)	Cases were white patients seen for breast cancer surgery at the University of lowa Hospitals between 1974 and 1978. Controls were patients without history of cancer from the general medicine and surgery wards, matched for age and hospital payment category. A trained interviewer administered a questionnaire to all subjects.	113 cases (32% users), 113 controls (45% users)	Estrogen use was defined as use for more than one month, Unadjusted RR 0.71 (0.34-0.1 1) Adjusted RR* 0.55 (p= 0.029) *adjusted for weight and height		

TABLE F-1: HRT and Breast Cancer Risk (Hospital-Based Case-Control Studies) (Page 6 of 10)

Author	Description of cases and controls	Number of cases and controls	Relationship of breast cancer to estrogen use [a,b]	Relationship of breast cancer to duration of estrogen use [a,b]	Relationship of breast cancer to dose, recency, and latency of estrogen use [a,b]
Horowitz (1984)	Cases and controls were postmenopausal women, age 45 or older, evaluated at Yale New Haven Hospital, Connecticut, between 1976 and 1979. Patients with clinical conditions making them unlikely to have received postmenopausal estrogens were excluded from control groups chosen to reduce the likelihood of ascertainment bias and detection bias. Four case control groups were compared. Group 1.150 breast cancer patients initially diagnosed by mammography were compared to 150 women with mammographically normal breasts. Group 2: same 150 breast cancer patients were matched with 150 women with benign breast disease by mammography. Group 3:107 breast cancer patients with initial diagnosis by breast biopsy were matched with 107 control patients with histologically benign disease. Group 4:257 breast cancer patients were matched to 257 control patients chosen from the medical or surgical wards of the hospital (conventional control group). Data were obtained from hospital and physician office records.	257 breast cancer cases, including 150 breast cancer cases diagnosed by mammography, and 107 breast cancer cases diagnosed by biopsy. Control group 1: 150 (normal by mammography) Control group 2: 150 (benign breast disease by mammography) Control group 3: 107 (histologically normal biopsy) Control group 4: 257 (hospitalized patients with other diagnoses) (conventional control group)	Estrogen use was defined as at least 0.3 mg/day of estrogen for at least three months. Group 1: O.R. 0.4 (0.3-0.7) Group 2: O.R. 0.5 (0.3-0.8) Group 3: O.R. 0.8 (0.5-1.4) Group 4: O.R. = 0.9 (0.5-1 .7) when only those medical records which had specific notations about use or nonuse of estrogens were used; O.R. = 3.3 (2.2-5.0) when those medical records with no specific notations about estrogen use were classified as nonusers.		

TABLE F-1: HRT and Breast Cancer Risk (Hospital-Based Case-Control Studies) (Page 7 of 10)

Author	Description of cases and controls	Number of cases and controls	Relationship of breast cancer to estrogen use [a,b]	Relationship of breast cancer to duration of estrogen use [a,b]	Relationship of breast cancer to dose, recency, and latency of estrogen use [a,b]
Kaufman (1984)	Cases and controls were from several hospitals in the United States and Canada. Cases were pre- and post-menopausal women younger than 70 years of age (median age 51) admitted to these hospitals between 1976 and 1981 with the diagnosis of breast cancer made no more than six months prior to admission. Controls were women less than 70 years of age (median age 51) who were admitted to these hospitals for malignant conditions judged to be unrelated to noncontraceptive estrogen, and with age within one decade of control subjects.	1,610 cases (925 postmenopausal), 1,606 controls (1 ,127 postmenopausal)	Estrogen use was defined as use at least 18 months prior to admission, Pre- and postmenopausal ever use of noncontraceptive estrogens: conjugated estrogens: 0.9 (0.7-1.1) nonconjugated estrogens: 0.8 (0.6-1 .1) all estrogens: 0.8 (0.5-1 .2) Premenopausal use of conjugated estrogen: 1.3 (0.6-2.9) Postmenopausal use of conjugated estrogen: 0.8 (0.7-1 .1)	Duration of conjugated estrogen use: Natural menopause: <1 year: 0.9 (0.5-1 .5) 1-4 years: 0.9 (0.5-1 .5) 5-9 years: 0.7 (0.4-1 .5) >10 years: 1.3 (0.6-2.8) Hysterectomy only: <1 year: 1.3 (0.5-3.3) 1-4 years: 1.2 (0.5-2.8) 5-9 years: 0.7 (0.2-1 .7) >10 years: 0.3 (0.1-1 .0) Hysterectomy and oophorectomy: <1 year: *0.4 (0,1 -1 .0)* 1-4 years: 0.8 (0.4-1 .6) 5-9 years: 1.1 (0.5-2.3) >10 years: 0.5 (0.2-1 .0)	Natural menopause: <1.25 mg: 1.2 *(0.5-2.5)* *>1.25* mg: *0.7 (0.3-1.5)* Hysterectomy: <1.25 mg: *0.7 (0.2-3.3)* *>1.25* mg: 0.4 (0.2-1 .0) Hysterectomy and oophorectomy: <1.25 mg: 2.0 (0.6-6.4) >1.25 mg: 0.5 (0.3-1 .0) Natural menopause: —all use within 10 yrs. before admission: 1.0 (0.6-1 .5) —all use ending >=10 yrs. before admission: 0.5 (0.3-1.1) —use spanning 10 yrs. before admission: 1.4 (0.8-2.4) —last use within 10 yrs. plus current use (use within past year): 0.6 (0.3-1 .2) Hysterectomy and oophorectomy: —use within 10 yrs. before admission: 1.0 (0.5-1 .8) —use ending >= 10 yrs. before admission: 0.3 (0.1 -0.8)[c] —use spanning 10 yrs. bef ore admission: 0.5 (0.3-1 .0) —use within 10 yrs. plus current use (use within past year): 1.2 (0.5-2.6)

TABLE F-1: HRT and Breast Cancer Risk (Hospital-Based Case-Control Studies) (Page 8 of 10)

Author	Description of cases and controls	Number of cases and controls	Relationship of breast cancer to estrogen use [a,b]	Relationship of breast cancer to duration of estrogen use [a,b]	Relationship of breast cancer to dose, recency, and latency of estrogen use [a,b]
Nomura (1986)	Cases were white women or women of Japanese ancestry, ages 45 to 74 (average age 57 for Japanese, 61 for white), diagnosed with breast cancer between 1975 and 1980 in one of seven hospitals in Oahu, Hawaii. One hospital control was selected for each case, matched for sex, race, age, Oahu residency, time of hospitalization, and hospital. Controls with a diagnosis of cancer were excluded. One neighborhood control was selected for each case, matched for sex, race, age and Oahu residency. Patients were interviewed.	161 white cases; 161 hospital controls, 159 neighborhood controls 181 Japanese cases; 183 hospital controls, 181 neighborhood controls	Japanese: 1.1 (0.7-1.6) compared with neighborhood controls, 1.0 (0.6-1 .4) compared with hospital controls Whites: 0.9 (0.5-1.3) compared with neighborhood controls; 0.7 (0.4-1 .1) compared with hospital controls	Whites: 1-12 me.: 0.9 (0.4-2.0) community controls; 0.5 (0.2-1.0) hospital controls 13-72 me.: 0.7 (0.4-1.5) community controls; 1.4 (0.6-2.9) hospital controls 73+ mo.: 1.3 (0.7-2.6) community controls; 0.8 (0.4-1 .6) hospital controls Japanese. 1-12 me.: 2.4 (1 .3-4.7) community controls; 1.0 (0.6-1.8) hospital controls 13-72 mo.: 0.7 (0.3-1.5) community controls; 0.6 (0.3-1 .2) hospital controls 73+ mo.: 1.9 (0.8-4.4) community controls; 1.2 (0.6-2.4) hospital controls	Recency (time since last use), Whites: <8 yrs.: 1.3 (0,6-2.8) community; 1.2 (0.6-2.6) hospital 8-16 yrs.: 0.7 (0.3-1.4) community, 0.5 (0.2-1 .0) hospital 16 + yrs.: 1.1 (0.6-2.2) community; 0.8 (0.4-1.5) hospital Japanese: <8 yrs.: 1,0 (0.5-1 .9) community; 0.8 (0.4-1.7) hospital 8-16 yrs.: 2.3 (1 .1-4.7) community; 1.1 (0.6-1 .9) hospital 16 + yrs.: 2.6 (1 .1-6.1) community, 1.0 (0.5-2.0) hospital
Kaufman (1991)	Followup on cohort described in Kaufman (1987). Cases were postmenopausal women ages 40 to 69 years (median age 59 years) diagnosed with breast cancer between 1980 and 1986 and hospitalized in one of several hospitals in seven U.S. and Canadian cities. Controls were postmenopausal women ages 40 to 69 years (median age 59 years) hospitalized with malignant and nonmalignant nongynecological conditions judged to be unrelated to estrogen use. Data were obtained form interviews and hospital records.	1,686 cases (18Y0 users); 2,077 controls *(17%* users)	RR 1.2 (1 .0-1.4) Type of estrogen: unopposed: 1.2 (1 .0-1.4) conjugated: 1.3 (1 .0-1.6) other estrogen. 1.3 (0.6-2.8) opposed by progestin: 1.7 *(0.9-3.3)*	< 1 year: 1,3 (1 ,0-1.8) 1-4 years: 1.2 (0.9-1.6) 5-9 years: 1.4 (0.9-2.2) 10-14 years: 1.0 (0.6-1.6) >15 years. 0.9 (0.4-1 .9)	<1.25 mg: 0.8 (0.4-1 .5) > 1.25 mg: 1,2 (0.7-2.0) mixed mg: 1.6 (0.6-4.0) Recency (time since last use): <12 mo.: 1.1 (0,7-1.6) 12-35 mo.: 1.3 (0.8-2.4) 36-59 mo.: 0.8 (0.4-1 .4) 60-119 mo.: 1.5 (1 ,0-2.2) >120 mo.: 1.2 (0,9-1 .6) Number of years since 5 years of use. <5 yrs.: 2.0 (0.9-4.2) 5-9 yrs.: 1.3 (0.9-2.1) 10-14 yrs.: 0.5 (0.2-1 .0) >15 yrs.: 1.3 (0.7-2.4)

TABLE F-1: HRT and Breast Cancer Risk (Hospital-Based Case-Control Studies) (Page 9 of 10)

Author	Description of cases and controls	Number of cases and controls	Relationship of breast cancer to estrogen use[a,b]	Relationship of breast cancer to duration of estrogen use[a,b]	Relationship of breast cancer to dose, recency, and latency of estrogen use[a,b]
Harris (1992)	Subjects were part of an ongoing study by the American Health Foundation and were selected for interview from hospitals in the New York City area from January 1987 to December 1989. Cases were women with newly diagnosed breast cancer. Control subjects did not have breast cancer and were matched with controls by age, hospital, and time of diagnosis.		< 5 years use: adjusted O.R. 2.0 (no c.i.) > 5 years use: adjusted O.R. 2.2 (no c.i.) (test for trend: $p < 0.02$)		

TABLE F-1: HRT and Breast Cancer Risk (Hospital-Based Case-Control Studies) (Page 10 of 10)

Author	Description of cases and controls	Number of cases and controls	Relationship of breast cancer to estrogen use[a,b]	Relationship of breast cancer to duration of estrogen use [a,b]	Relationship of breast cancer to dose, recency, and latency of estrogen use [a,b]
La Vecchia (1992)	European multicenter study (1986 study updated to Dec. 1990); cases were ages 26 to 74 years (median age 56 years) with histologically confirmed breast cancer admitted to one of several hospitals in Northern Italy. Controls were 25 to 74 years (median age 56 years) admitted to hospitals in Northern Italy for acute conditions that were not hormonal, gynecological, or malignant. Cases and controls were questioned by trained interviewers. Results include both pre- and postmenopausal women, Subjects were followed from 1983 to 1990	3,037 cases (4.9% users); 2,569 controls (3.5% users)	RR 1.4 (1.1-1.8) adjusted for age Adjusted RR * 1.3 (1 .0-1 .8) (This represents a lower risk estimate than the 1986 study, with regression towards the mean overall results from other studies.) Updated results may be overestimated by using orthopedic controls, which may be inversely related to estrogen use (but separate analyses by diagnostic subcategories did not lead to any appreciable difference in risk). Risk estimates may be affected by higher socioeconomic status of users but risk estimates were not modified by alliance of indicators of socioeconomic status. *Adjusted for age, geographic area, marital status, education, benign breast disease, family history of breast cancer, nulliparity, age at first birth, age at menarche, type of menopause, age at menopause, body mass index, and oral contraceptive use	<3 years, RR 1,2 (0.9-1 ,7) adjusted for age Adjusted RR 1.2 (0.9-1 .7) >3 years, RR 1,5 (0,9-2.5) adjusted for age Adjusted RR 1.5 (0,9-2.6) (test for trend, p < 0.05)	Recency (time since last use). <10 yrs.: RR 1,3 (0.9-1 .5) adjusted for age Adjusted RR: 1.2 (0.8-1 .8) >10 yrs.: RR 1.5 (1.1 -2,3) adjusted for age Adjusted RR: 1.5 (1 .0-2.3) Latency (time since first use). <10 yrs.: RR 1,5 (1 ,0-2.3) adjusted for age Adjusted RR 1.3 (O 8-2.0) >10 yrs.: RR 1.4 (1 ,0-2.0) adjusted for age Adjusted RR 1.4 (1 .0-2.0)

[a]Unless otherwise specified, measured relationships are relative risk of breast cancer in HRT
b 95% confidence interval is given in parentheses
C This low relative risk may be due to chance or due to the fact that women who have ovaries removed at a young age' 1) have lower risk of breast cancer, (2) are more likely to be prescribed estrogen, generally for a short period of time
KEY: C.I. = confidence interval; NS = not statistically significant; O R = odds ratio; RR = relative risk

SOURCE: Office of Technology Assessment, 1995

TABLE F-2: HRT and Breast Cancer Risk (Population-Based Case-Control Studies) (Page 1 of 10)

Author	Description of cases and controls	Number of cases and controls	Relationship of breast cancer to estrogen use [a,b]	Relationship of breast cancer to duration of estrogen use [a,b]	Relationship of breast cancer to dose, recency, and latency of estrogen use [a,b]
Mack (1 975)	Cases and controls were white female residents of a retirement community in Southern Los Angeles, median age 71. Cases were diagnosed with breast cancer between 1971 and 1975. Controls were selected from a roster of all women in the community, matched with cases for age and date of entry into the community. Information was gathered from questionnaires and medical records.	99 cases breast cancer, 396 controls (26% ever users of estrogen among controls)	Ever use 1.6 (no c.i.) Use at least 5 years before diagnosis. 1.7 (no c.i.)		
Casangrande (1976)	Two groups of subjects were selected. Group I was composed of case-control pairs who were white residents of Los Angeles County Cases were between 50 and 64 years of age at diagnosis of breast cancer, diagnosed between 1969 and 1972. A control, matched for age and socioeconomic status, was selected from the outpatient rosters of each index cases' referring physician. Group II cases were white patients whose breast cancers were diagnosed between 1972 and 73, and who were between the ages of 50 and 59 at disease diagnosis, lived in SIX middle class white health districts of eastern Los Angeles Cases were matched with healthy control neighbors ages 50 to 59 years	Group 1: 60 cases; 53 controls Group II 33 cases, 27 controls	For women with natural menopause. Group 1: unadjusted RR 0.47 (no c.i.); adjusted RR* 0.75 Group 11: unadjusted RR 2,15 (no c.i.); adjusted RR* 3.1 Pooled estimate, 1.2 (p - 0.40) *adjusted for age at menopause		

TABLE F-2: HRT and Breast Cancer Risk (Population-Based Case-Control Studies) (Page 2 of 10)

Author	Description of cases and controls	Number of cases and controls	Relationship of breast cancer to estrogen use [a,b]	Relationship of breast cancer to duration of estrogen use [a,b]	Relationship of breast cancer to dose, recency, and latency of estrogen use [a,b]
Ross (1980)	Cases were white women diagnosed with breast cancer between 1971 and 1977, between 50 and 74 years of age, from two Los Angeles retirement communities. Two postmenopausal controls were selected for each case from the same community, matched for age, race, move-in date, and marital status. Estrogen use was ascertained from interviews, medical records, and pharmacy records.	138 cases of breast cancer, 281 controls	Estrogen use was defined as use beginning more than 4 months preceding diagnosis. All: 1.1 (0.8-1.9) Ovaries intact: 1.4 (0.7-2.4) Ovaries removed. 0.8 (0.5-3.5)	> 7 yrs.: 1.8 (test for trend. p = 0.02)	Total mg dose (TMD) (= daily dose x duration) No exposure (O TMD). ovaries intact. 1.0 ovaries removed: 1.0 all. 1.0 Low exposure (< 1.500 TMD): ovaries intact: 0.9 (0.4-1.7) ovaries removed: 0.9 (0.2-3.2) all: 0.8 (0.5-1 .5) High exposure (>= 1,500 TMD) (3 yrs. x 1.25 mg/d): ovaries intact: 2.5 (1 .2-5.6) ovaries removed: 0.7 (0.2-2.4) all: 1.9 (1 .0-3.3)
Hoover (1981)	Cases were all women with breast cancer identified from the tumor registry of Kaiser Foundation Health Plan of Portland, Oregon occurring from January 1969 to December 1975. Controls were drawn from 5% of a random sample of all members of the Kaiser Foundation Health Plan. Information was gathered from medical records. Average age of cases and controls was 57.	345 cases; 611 controls (69% estrogen users)	Ever use: 1.4 (1 .0-2.0) Natural menopause: 1.3 (0.8-2.1) Oophorectomized women. 1.5 (0.3-6.6)	Number of prescriptions noted, 0.1.00 1 : 1.1 2-4: 1.3 5-9. 1.8 > 10: 1.8 (test for trend: p = 0.013) Years between first and last prescription. none 1.00 <4, 1,4 >5, 1.7 (test for trend. D = 0.022)	Usual daily dose: nonuser: 1.00 < 1 .25mg, 1.4 > 1.25mg, 1.8 (test for trend. p = 0.005)

TABLE F-2: HRT and Breast Cancer Risk (Population-Based Case-Control Studies) (Page 3 of 10)

Author	Description of cases and controls	Number of cases and controls	Relationship of breast cancer to estrogen use[a,b]	Relationship of breast cancer to duration of estrogen use [a,b]	Relationship of breast cancer to dose, recency, and latency of estrogen use [a,b]
Hiatt (1 984)	Study subjects were identified from list of operations performed in all Northern California Kaiser Foundation Health Plan hospitals between 1953 and 1979. Cases were identified by hospital discharge records. Controls were chosen from women with same age, year of oophorectomy, and date of entry into health plan membership. Information was gathered from medical records.	119 cases, 119 controls (90% estrogen users)	RR 0.7 (0.3-1 .6)	Chart of notations of estrogen use >=5 yrs.: 2.1 (1 .2-3,6) Duration >= 3 yrs.: 1.8 (0.9-3.6)	Three or more years since first use, 0.8 (0.4-1.9)
Brinton (1986)	Subjects for the study were from a multicenter breast cancer screening program. Cases were white women who underwent natural or surgical menopause at least three months prior to the diagnosis of breast cancer; cases were diagnosed between 1973 and 1980. Controls were chosen from women who did not have biopsy during course of screening and were matched to the cases for race, age, time of entry, medical center and length of continuation in the program. Information was gathered through home interviews.	1,960 cases; 2,258 controls	1.03 (0.9-1.2)	<5 yrs.: 0.89 (0,8-1.0) 5-9 yrs.: 1.09 (0.9-1.3) 10-14 yrs.: 1.28 (0.9-1 .6) 15-19 yrs.: 1.24 (0.9-1 .8) 20+ yrs.: 1.47 (0.9-2.3) (test for trend: p < 0.01)	Premarin 0.3 mg: <10 yrs. use: 1.04(NS) 10+ yrs. use: 0.76(NS) total: 0.99 (0.7-1 .4) Premarin 0.625 mg: <10 yrs. use: 0.90(NS) 10+ yrs. use: 1.94 (p < 0.05) total: 1.05 (0.8-1 .3) Premarin 1.25 mg: <10 yrs. use: 0.94(NS) 10+ yrs. use: 1.13(NS) total. 1.02 (0.9-1.2) Premarin 2.5 mg: <10 yrs. use: 0.77(NS) 10+ yrs. use: 1.00(NS) total: 0.84 (0.5-1.4) Years since initial use: <1 o: 1.03 (0.9-1 .2) 10-14: 1,15 (0.9-1.4) 15-19: 0.95 (0.7-1.2) 20+: 0,97 (0.7-1 .2) (test for trend. p = 0.45)

TABLE F-2: HRT and Breast Cancer Risk (Population-Based Case-Control Studies) (Page 4 of 10)

Author	Description of cases and controls	Number of cases and controls	Relationship of breast cancer to estrogen use [a,b]	Relationship of breast cancer to duration of estrogen use [a,b]	Relationship of breast cancer to dose, recency, and latency of estrogen use [a,b]
McDonald (1986)	Cases were white female residents of King County, Washington, ages 50 to 74, in whom breast cancer was diagnosed from July 1977 through August 1978, cases were identified from a cancer reporting system. Controls were white female residents of King County, 50 to 74 years old, without breast cancer. All cases and controls were interviewed.	183 cases, 531 controls	Estrogen use was defined as at least 1 yr. of estrogen use Overall. 0.74 (0.51 -1 .08) Natural menopause O 76 (0.46-1 .26) Hysterectomy with oophorectomy: 1.28 (0.43-3.80) "[S]ome variation In proportions was present between different hysterectomy-oophorectomy subgroups. However, each of these differences could easily have been due to chance "	1-5 yrs.: O 83 >6 yrs.: 0,68 (test for trend p = 0.06)	Never: 1.00 0.2-1.0 mg: 0.55 > 1.0 mg: 0,81 (test for trend. p = 0.22) Recency (time since last use): Never 1,00 current user or <= 5 yrs.: 0.75 >6 yrs.: 0.76 (test for trend. p = 0.14) Latency (time since first use). Never. 1.00 <10 yrs.: 0,73 > 10 yrs.: 0.74 (test for trend: p=O.11)
Hunt (1987)	Subjects were women, ages 45 to 54 receiving hormonal replacement therapy, recruited from 21 menopause clinics around Britain. Recruitment was both retrospective and prospective. Subjects were followed from 1978 to 1982. Two controls were selected for each case from cohort.	53 breast cancer cases, 106 controls		Adjusted' RR 12-30 months 1.0 (no c.i.) 31-48 months 48 (1 .5-156) 49-72 months 5.3 (1 .4-202) >73 months, 36 (0,9-1 5,0) *adjusted for uterine and ovarian status	

TABLE F-2: HRT and Breast Cancer Risk (Population-Based Case-Control Studies) (Page 5 of 10)

Author	Description of cases and controls	Number of cases and controls	Relationship of breast cancer to estrogen use[a,b]	Relationship of breast cancer to duration of estrogen use [a,b]	Relationship of breast cancer to dose, recency, and latency of estrogen use [a,b]
Wingo (1 987)	CASH study, all subjects were postmenopausal women enrolled from eight different geographic areas in the United States. Cases were women 25 to 54 years old with cancer diagnosed between 1981 and 1982 and Identified through the SEER cancer registry. Controls were selected from the same geographical area by random digit dialing of residential telephone numbers. Information was gathered through interviews.	1,369 cases, 1,645 controls	Adjusted RR for users of more than 3 months versus nonusers. 1,0 (0,9-1.2) All women. 1.0 (0.9-1.2) ever users versus nonusers Hysterectomy and bilateral oophorectomy: ever users versus nonusers: 1.3 (0.9-1.9) Hysterectomy only ever users versus nonusers: 1.1 (0.8-1 .5) Natural menopause: ever users versus nonusers: 0.8 (0.6-1 .1)	All women < 1 year 1,0 (0,7-1 .3) 1-4 yrs.: 1.1 (0.8-1.3) 5-9 yrs.: 1.1 (0.8- 1.5) 10-14 yrs.: 0.8 (0.5-1.3) 15-19 yrs.: 1.3 (0.6-2.6) >20 yrs.: 1.8 (0.6-5.8) (test for trend. p = 0.7) Hysterectomy with bilateral oophorectomy. <1 year: 1,6 (0.9-2,8) 1-4 yrs.: 1.3 (0.9-2.0) 5-9 yrs.: 1.1 (0.7-1 .8) 10-14 yrs.: 1.5 (0.8-2.9) >15 yrs.: 1.7 (0,7-4,4) (test for trend: p = 0.9) Hysterectomy only. <1 year: 0.9 (0.6-1 .5) 1-4 yrs.: 1.1 (0.8-1 .6) 5-9 yrs.: 1.6 (1 .0-2.8) 10-14 yrs.: 0.6 (0.3-1 .2) >15 yrs.: 2.0 (O. 7-5.5) (test for trend: p = 0.7) Natural menopause. < 1 year: 0.8 (0.4-1 .4) 1-4 yrs.: 0.9 (0.6-1 .3) >5 yrs.: 0.7 (0.3-1.4) (test for trend. p = 0.6)	Dose (ever users compared with never users) (milligram-months): <25 1 1 (0,8-1 .5) 25-499. 1.3 (0.9-1.9) 50-749. 1.1 (0.7-1.8) 75-99 .9.1.9 (1.1 -3.3) > 100: 0.8 (0.6-1 .2) (test for trend p = 0.03) Recency (time since last use): <1 yr.: 1.0 (0.8-1.2) 1-4 yrs.: 1.2 (0.9-1 .6) 5-9 yrs.: 1.1 (0.8-1 .6) >10 yrs.: 1.0 (0.5-1 .8) (test for trend: p = 0.06) Latency (time since first use): All women: < 1 year: *0.9 (0.5-1.5)* 1-4 yrs.: 1.1 (0.8-1.4) 5-9 yrs.: 1.1 (0.8-1.4) 10-14 yrs.: 0.9 (0.7-1 .3) 15-19 yrs.: 1.1 (0.6-2.1) >20 yrs.: 1.7 (0,8-3,7) (test for trend: p = 0.8)

TABLE F-2: HRT and Breast Cancer Risk (Population-Based Case-Control Studies) (Page 6 of 10)

Author	Description of cases and controls	Number of cases and controls	Relationship of breast cancer to estrogen use [a,b]	Relationship of breast cancer to duration of estrogen use [a,b]	Relationship of breast cancer to dose, recency, and latency of estrogen use [a,b]
Ewertz (1 988)	Cases were pre- and postmenopausal women below 70 years of age diagnosed with breast cancer between 1983 and 1984, Identified from the files of a Danish clinical trial of breast cancer therapy and from a Danish cancer registry. Controls were a random sample of women from the general population, stratified for age, identified from a Danish population registry. Data were collected by mailed questionnaire.	1,484 cases (56.2% postmenopausal), 1,334 controls (58.9% postmenopausal)	Menopausal.' 1,16 (0.64-2.1 1) Post-menopausal" 1,28 (0.96-1 .71) Artificial menopause. 1.04 (0.69-1 .57) ● "menopausal" defined as natural menopause within 5 years of diagnosis **"postmenopausal" defined as natural menopause more than 5 years before diagnosis "Exposure to estrogen or progestagen, alone or in combination-type therapy, did not affect the breast cancer risk. Sequential therapy with oestrogen and progestagen ., was associated with an increased risk of borderline statistical significance (RR=1.36 (0.98-1 .87))."	Menopausal: <3 years, 1.08 (0,51 -2.27) 3-5 yrs.: 1.10 (0.38-3.21) 6+ yrs.: 1.57 (0.55-4.44) (test for trend: p = 0.44) Postmenopausal. <3 yrs.: 0,89 (0,56-1 .41) 3-5 yrs.: 0.93 (0.52-1 .68) 6-8 yrs.: 1.82 (0.98-3.37) 9-11 yrs.: 1.34 (0.70-2.54) 124 yrs.: 2.32 (1 .31 -4.12) (test for trend: p = 0.002) Artificial menopause: <3 yrs.: 1,01 (0.55-1 .85) 3-5 yrs.: 0.81 (0.39-1 .70) 6-8 yrs.: 1.52 (0.65-3.53) 9-11 yrs.: 1.44 (0.70-2.96) 12+ yrs.: 0.88 (0.48-1 ,64) (test for trend p > 0.5)	Recency (time since last use). Menopausal: <3 yrs.: 1,59 (0,80-3,16) 3+ yrs.: 0.53 (0.19-1 .45) Postmenopausal: <3 yrs.: 1.48 (1 .01 -2.15) 3-5 yrs.: 1.13 (0.56-2.30) 6-8 yrs.: 0.99 (0.52-1 .88) 9+ yrs.: 1.18 (0.68-2.02) Artificial menopause: <3 yrs.: 1.09 (0.70-1 .71) 3-5 yrs.: 0.57 (0.21-1 .51) 6-8 yrs.: 2.76 (0.73-10.5) 9+ yrs.: 0.91 (0.39-2.11) Latency (time since first uses): Menopausal: <6 yrs.: 1,84 (0,84-4,04) 6+ yrs.: 0.57 (0.25-1 .30) Postmenopausal: <6 yrs.: 0,95 (0.45-2,02) 6-8 yrs.: 1.10 (0.60-2.04) 9-11 yrs.: 103 (0.62-1 .73) 12+ yrs.: 1.74 (1.19-2 55) Artificial menopause. <6 yrs.: 1,07 (0,53-2.16) 6-8 yrs.: 1,48 (0.71-3.09) 9-11 yrs.: 127 (0.64-2 49) 12+ yrs.: 0.89 (0.52-1 .50)

TABLE F-2: HRT and Breast Cancer Risk (Population-Based Case-Control Studies) (Page 7 of 10)

Author	Description of cases and controls	Number of cases and controls	Relationship of breast cancer to estrogen use[a,b]	Relationship of breast cancer to duration of estrogen use [a,b]	Relationship of breast cancer to dose, recency, and latency of estrogen use [a,b]
Rohan (1988)	Cases were women from Adelaide, South Australia, with breast cancer reported to a cancer registry between 1982 and 1984, and who were 20 to 74 years old at the time of diagnosis. Controls were women from Adelaide with no history of breast cancer, identified from electoral rolls. Information was obtained through questionnaires. Reported here is information only on those women who were postmenopausal (no menses within 12 months or surgical menopause).	281 cases; 288 controls	Unadjusted RR 0.88 (0.57-1 .37) Adjusted RR .1.03 (0.62-1 .69) Women with bilateral oophorectomy: 0.30 (0.09-0.94) adjusted for age Natural menopause: 1.01 (0.69-1 ,47) adjusted for age * adjusted for years of educalion, practice of breast self-examination, history of breast cancer in first degree relative, age at last menstrual period, and history of bilateral oophorectomy	<24 me,, unadjusted, 1.02 (0,61-1 .72) adjusted: 0.99 (0.56-1 .76) >24 me,, unadjusted: 0.61 (0.29-1 .31) adjusted: 0.94 (0.40-2.21) A relatively small number of women used exogenous estrogens and only a minority reported relatively long durations of use	Recency (time since last use): <= 2 yrs.: unadjusted. 0.85 (0.32-2.25) adjusted. 1.25 (0.44-3.58) >2 yrs.: unadjusted, 0.90 (0.54-1 .48) adjusted: 0.88 (0.51 -1 .54) Latency (time since first use):<= 15 years since first use: unadjusted: 0.80 (0.44-1 .45) adjusted: 0.79 (0.41-1 ,55) >15 years, unadjusted: 1.10 (0.58-2.08) adjusted: 1.27 (0.63-2.54) > 15 years since first and estrogen therapy >=24 me.: 1.54 (0.43-5.45) Age at first use: <45 y.o.: unadjusted: 0.64 (0.31-1 .33) adjusted. 0.79 (0.35-1 .80) >45 y.o.: unadjusted: 1.12 (0.66-1 .92) adjusted. 1 12 (0.61-2.04)

TABLE F-2: HRT and Breast Cancer Risk (Population-Based Case-Control Studies) (Page 8 of 10)

Author	Description of cases and controls	Number of cases and controls	Relationship of breast cancer to estrogen use[a,b]	Relationship of breast cancer to duration of estrogen use[a,b]	Relationship of breast cancer to dose, recency, and latency of estrogen use[a,b]
Bergkvist (1989)	Women who had been prescribed estrogens for conditions related to the menopause were identified through records of the pharmacies in the health care region around Uppsala, Sweden. Recruitment began in April 1977 and ended in March 1980 and subjects were followed for an average of 6 years. Cases were women in the cohort who developed breast cancer. Controls were women with six months or less of estrogen use, were selected from the subcohort, and were matched for year of birth and year of inclusion into the cohort.	207 breast cancer cases (one to five controls matched to each case)		Adjusted O.R.: < 6 mo.: 1.0 7-36 mo.: 1.0 (0.6-1.6) 37-72 mo.: 1.2 (0.7-2.0) 73-108 mo.: 1.5 (0.8-2.9) > 109 mo.: 2.3 (1.1-4.8) (test for trend: p = 0.02) *Odds ratio was adjusted for education, previous breast biopsy for benign breast disease, and type of menopause.	
Folsom (1990)	86-1987). Cases were women with incident breast cancer. Controls were randomly selected participants in the survey.	229 cases; 1,839 controls	Estrogen replacement therapy use: <5 years: 86% of cases, 90% of controls >5 years: 14% of cases, 10% of controls No statistical analysis of the data was presented.		

TABLE F-2: HRT and Breast Cancer Risk (Population-Based Case-Control Studies) (Page 9 of 10)

Author	Description of cases and controls	Number of oases and controls	Relationship of breast cancer to estrogen use [a,b]	Relationship of breast cancer to duration of estrogen use [a,b]	Relationship of breast cancer to dose, recency, and latency of estrogen use [a,b]
Palmer (1991)	Cases were women under age 70 who had breast cancer diagnosed more than six months before interview, identified at a major cancer treatment hospital in metropolitan Toronto between 1982 and 1986. Controls were identified from tax assessment rolls of all residents of Ontario. Two controls were matched to each case for age and neighborhood; 41 percent of cases and 42 percent of controls were pre- or postmenopausal. Cases and controls were interviewed in their homes.	607 breast cancer cases; 1,214 controls	Estrogens alone: 1.0 (0.7-1.3) Estrogen plus progesterone: 0.6 (0.2-2.0)	Conjugated estrogens. <1 yr.: 0.9 (0,5-1 .7) 1-4 yrs.: 0.7 (0.4-1 .3) 5-9 yrs.: 0.8 (0.4-1 .6) 10-14 yrs.: 0.6 (0.2-1 .8) >15 yrs.: 1.4 (0,6-3,3)	Recency (time since last use). Never: 1.0 <1 yr.: *0.4 (0.2-0,9)* *1-2* yrs.: 5.2 (2.0-13) 3-4 yrs.: 1.0 (0.3-3.1) 5-9 yrs.: 0.4 (0.2-1 .1) >10 yrs.: 0.8 (0.4-1.4) Latency (time since first use): Never: 1.0 Less than 5 yrs. total use and < 10 yrs. since first use. 0.8 (0.4-1 .5) 10-19 yrs.: 0.9 (0.5-1 .8) >20 yrs.: 0.5 (0.2-1 .6) Five or more years total use and < 10 yrs. since first use: 0.9 (0.3-2.5) 10-19 yrs.: 0.5 (0.2-1 .0) >20 yrs.: 2.1 (0,9-5.0)
Yang (1992)	Cases were all British Columbia women under 75 years of age who were diagnosed with breast cancer during 1988 and 1989. Controls were drawn from voter registration lists from the same province, and were matched with cases on the basis of age. Analysis included only postmenopausal women. Information was gathered by mailed questionnaire.	669 cases; 685 controls	O.R. 1.0 (0.8-1 .3) for ever use of unopposed estrogen O.R. 1.2 (0.6-2.2) for ever use of estrogen and progesterone	Long-term use (>= 10 years): O.R. 1.6 (1 .1-2.5)	Current use: O.R. 1.4 (1 .0-2.0)

TABLE F-2: HRT and Breast Cancer Risk (Population-Based Case-Control Studies) (Page 10 of 10)

Author	Description of cases and controls	Number of cases and controls	Relationship of breast cancer to estrogen use [a,b]	Relationship of breast cancer to duration of estrogen use [a,b]	Relationship of breast cancer to dose, recency, and latency of estrogen use [a,b]
Weinstein (1993)	Cases were female residents of Long Island, NY, aged 20 to 79, who were diagnosed with breast cancer from January 1984 to December 1986. Age- and county-matched controls were selected from driver's license files.	1,436 cases; 1,419 controls	There was no significant association between ever-use of HRT and breast cancer risk.	There was no significant association of risk with duration of use.	There was no significant association of HRT with recency of estrogen use. There was a significant increased risk of breast cancer in women with 10 to 19 years since first exposure.

[a] Unless otherwise specified, measured relationship is relative risk of breast cancer in HRT.
[b] 95% confidence interval is given in parentheses.

KEY: CI, = confidence interval; NS = not statistically significant; O R = odds ratio; RR = relative risk.

SOURCE: Office of Technology Assessment, 1995.

TABLE F-3: HRT and Breast Cancer (Cohort Studies) with Internal Controls (Page 1 of 6)

Author	Description of study	Number of study subjects	Relationship of estrogen use to breast cancer risk	Relationship of duration of estrogen use to breast cancer risk[a,b]	Relationship of dose, recency, and latency of estrogen to breast cancer risk[a,b]
Thomas (1982)	White women who were initially treated for biopsy-proven benign breast diseases from 1942 to 1975 in a single private surgery practice were followed through 1976 for development of breast cancer. Patients were followed up through letters, phone calls, clinic records, and death certificates. Average follow-up was 12,9 years.	1,439 women (66 cases breast cancer) (504 estrogen users)	Unadjusted RR 1.80 (1 ,04-3.10) adjusted RR 1.84 (1 ,05-3,23) There was no variance for age or year of first use.	No evidence was seen of an increased relative risk of breast cancer with increased duration of estrogen use.	
Bush (1983)	Participants were white women, aged 40 to 69 years at baseline, and followed for an average of 5.5 years. All women in the cohort were participants in the Lipid Research Clinics Program Follow-up Study, conducted in 10 North American Clinics between 1972 and 1976. All subjects were examined at initiation, and were followed with clinic visits and by review of death certificates. Information on decedents was gathered from medical records and family members.	2,270 white women (593 users, 1,677 nonusers)	Breast cancer deaths: users: O nonusers. 12 No statistical analysis of breast cancer deaths was provided.		
Petitti (1987)	Walnut Creek Contraceptive Drug Study; subjects were women aged 18 to 54 recruited from December 1968 to February 1972. All subjects received a history and physical exam at initiation and were followed by subsequent exam or questionnaire through 1977 Until the end of 1983, deaths were Identified through the California Death Index Users of oral contraceptives were excluded from this analysis.	3,437 women who never used oral contraceptives or estrogen; 2,656 women who had used estrogens, but not oral contraceptives	Risk of breast cancer death in users 0.8 (O 4-1.8) adjusted for age		

TABLE F-3: HRT and Breast Cancer (Cohort Studies) with Internal Controls (Page 2 of 6)

Author	Description of study	Number of study subjects	Relationship of estrogen use to breast cancer risk	Relationship of duration of estrogen use to breast cancer risk[a,b]	Relationship of dose, recency, and latency of estrogen to breast cancer risk[a,b]
Bergkvist (1989)	Women who had been prescribed estrogens for conditions related to the menopause were identified through records of the pharmacies in the health care region around Uppsala, Sweden. Recruitment began in April 1977 and ended in March 1980 and subjects were followed for an average of 6 years. Expected numbers of breast cancer cases were estimated according to incidence rates of breast cancer in the region. Median age of women in the cohort was 53.7 at time of inclusion into study. Information was gathered by mailed questionnaire from a subcohort of 1 in 30 women randomly chosen from the cohort.	23,224 women age 35 and older who had filled at least one prescription for estrogen; 253 breast cancer cases	RR 11 (1 .0-1 .3) Study suggested there was no protection from the addition of progesterone.	All HRT users. <6 mos.: *0,7 (0,4-1 .0)* 7-36 mos.: 1.1 (0.9-1 .4) 37-72 mos.: 1.0 (0,8-1 .4) 73-108 mos: 1.3 (0.9-1 .9) > 109 mos,: 1.7 (1,1 -2,7) estrogen only. <6 mos,: 0.8 (0,5-1 ,4) 7-36 mos.: 1.1 (0.8-1 .5) 37-72 mos.: 0.9 (0.6-1 .3) 73-108 mos.: 0.9 (0.5-1 .6) >109 mos,. 1,8 (1 ,0-3.1) estrogen plus progesterone.' <6 mos.. 0.5 (0,2-1 .8) 7-36 mos.: 0.7 (0.3-1 .3) 37-72 mos.: 0.9 (0.3-2.6) 73-108 mos,: 4.4 (0,9-22.4) >109 mos,: (no estimate)	

*Only a small number of women received combination therapy, so confidence Intervals are wide

TABLE F-3: HRT and Breast Cancer (Cohort Studies) with Internal Controls (Page 3 of 6)

Author	Description of study	Number of study subjects	Relationship of estrogen use to breast cancer risk	Relationship of duration of estrogen use to breast cancer risk[a,b]	Relationship of dose, recency, and latency of estrogen to breast cancer risk[a,b]
Mills (1989)	Subjects were white Seventh-Day Adventist women, residing in California, who completed a questionnaire and who were followed for 6 years, from 1976 and 1982. Mean age of cohort in 1976 was 55,4 years. Information was gathered from annual questionnaires, tumor registries and for cases, from medical records.	20,341 women in cohort (80% postmenopausal at study initiation) (66% ever users of HRT); 215 cases of breast cancer	Unadjusted RR 1.67 (1.1 7-2.39) adjusted RR' 1.39 (1 ,00-1 .94) *adjusted for age, ages at menarche, first birth, and menopause, Quetelet's Index, maternal breast cancer, and a history of previous benign breast disease natural menopause: 1.74 (1 .10-2,74) hysterectomy, 1.30 (0.78-2.18)	*<1 yr.: 2,28* (1 .38-3.79) 1-5 yrs.: 1.56 (0.95-2.56) 6-10 yrs.: 2.75 (1.64-4.64) 10+ yrs.: 1.53 (0.92-2.54) There was no strong increase in risk with duration of HRT.	*<1 yr,: 2.28* (1 .38-3.79) 1-5 yrs.. 1.56 (0.95-2.56) 6-10 yrs.. 2.75 (1 .64-4.64) 10+ yrs.. 1.53 (0.92-2.54) There was no strong increase in risk with duration of HRT.

TABLE F-3: HRT and Breast Cancer (Cohort Studies) with Internal Controls (Page 4 of 6)

Author	Description of study	Number of study subjects	Relationship of estrogen use to breast cancer risk	Relationship of duration of estrogen use to breast cancer risk[a,b]	Relationship of dose, recency, and latency of estrogen to breast cancer risk[a,b]
Colditz (1 990)	Female registered nurses 30 to 55 years of age completed a mailed questionnaire. Follow-up questionnaires were mailed every 2 years. Data were gathered between 1976 and 1986. Only those RNs that were postmenopausal are included in these results.	23,607 postmenopausal female registered nurses; 722 cases of breast cancer	Current use: 1.40 (1 ,16-1 .67)	Current users: 1-11 mos.: 1,28 (0.8-2.1) 12-23 mos.: 1,32 (0.8-2.2) 24-35 mos.: 1.44 (0.9-2.2) 36-59 mos.. 1.26 (0.9-1 .9) 60-119 mos.. 1.62 (1 .2-2,1) 120-179 mos.: 1.28 (0.8-2.0) >180 mos,: 1,19 (0,6-2.2) past users: 1-11 mos.: 1.00 (0.7-1 .4) 12-23 mos.: 1.05 (0.7-1 .5) 24-35 mos.: 0.65 (0.4-1 .1) 36-59 mos.. 1.02 (0.7-1 .5) 60-119 mos.: 1.05 (0.7-1 .5) 120-179 mos.: 0.92 (0.5-1.7) >180 mos.: 0,79 (0,3-2.5)	Current users 0.3 mg/d:1 .55 (1 .0-2.5) 0.625 mg/d: 1.42 (1 .0-1 .9) 1,25 mg/d:1.48 (1 .0-2.2) <1,25 mg/d: *2.27* (1 .0-5,3) Trend with increasing dosage was not significant (test for trend: p = 0.56). current use. 1.40 (1 .16-1 .67) past use. 0.99 (0.82-1.19) time since last use: current 1.36 (1.1 1-1 ,67) 1-11 mos.. 1.62 (0.98-2.67) 12-35 mos.. 1.09 (0.79-1 .50) 36-59 mos.: 0.89 (0.60-1 .31) 60-119 mos.. 0.93 (079-1 .47) > 120 mos. 0,70 (0.45-1 .10)

TABLE F-3: HRT and Breast Cancer (Cohort Studies) with Internal Controls (Page 5 of 6)

Author	Description of study	Number of study subjects	Relationship of estrogen use to breast cancer risk	Relationship of duration of estrogen use to breast cancer risk[a,b]	Relationship of dose, recency, and latency of estrogen to breast cancer risk[a,b]
Henderson (1991)	Prospective study of postmenopausal female residents of Leisure World Retirement Community in Southern California. Residents are predominantly white, moderately affluent, and well-educated. Median age of cohort was 73 at study initiation. Study was initiated in 1981, average follow-up is 7.5 years. Information was gathered through mailed questionnaires and death registries.	8,881 postmenopausal women (the number of deaths from breast cancer was not specified in report) (57% ever estrogen users)	RR 0,81 (c. I. not reported) for breast cancer deaths in ever users versus never users of estrogen	After adjusting for age, there was no evidence of increased risk with increasing duration of use among current users (test for trend: p =0.41) or past users (test for trend p = 0.46).	Breast cancer incidence current use. RR 1.33 (1,1 2-1 ,57) adjusted for age past use: RR 0.90 (0.77-1 .04) adjusted for age
Colditz (1 992)	Subjects were female registered O nurses 30 to 55 years of age 1976. Reported here are results of 12 years of follow-up. Data was obtained by questionnaires mailed every two years, cases of breast cancer were confirmed by review of pathology reports and hospital records.	480,665 person-years of follow-up, 1,050 incident cases of breast cancer	Ever use 1.08 (0.96-1 .22) adjusted for age current use of hormones: 1.33 (1 .12-1 .57) adjusted for age current use of unopposed estrogen: 1,42 (1.1 9-1 .70) current use of estrogen and progesterone: 1.54 (0.99-2.39) current use of progesterone alone: 2.52 (0.66-9.63) current use of conjugated estrogens 1,42 (1 .19-1 .20) current use of estrogen/ progestin 1.54 (0.99-2.39) current use of estrogen/ testosterone 2.45 (0.95-6.35)		

TABLE F-3: HRT and Breast Cancer (Cohort Studies) with Internal Controls (Page 6 of 6)

Author	Description of study	Number of study subjects	Relationship of estrogen use to breast cancer risk	Relationship of duration of estrogen use to breast cancer risk[a,b]	Relationship of dose, recency, and latency of estrogen to breast cancer risk[a,b]
Schairer (1994)	Subjects were participants in the Breast Cancer Detection Demonstration Project, a breast cancer screening program conducted between 1973 and 1980. (The analysis reported here included all women who did not have a menses for at least 3 months prior to an interview. Reported here is followup through 1989). Information was collected by telephone interviews mailed questionnaires, and pathology reports. Average age at start of followup was 57.4 years. Mean duration of followup was 6,2 years.	**49,017** (1,185 breast cancer cases) (46.2 of person-years in study involved ERT, 6% with combined PERT)		Current ERT users: 1.3 (1 .1-1 .5) past users: 0.9 (0,8-1 .1) Current PERT users: 1.2 (0.9-1 .6) past users: 1.4 (1 .0-2.0) estrogen alone: 1.0 (0.9-1 .2) estrogen and progestin. 1.2 (1 ,0-1 .6) in situ tumors only: estrogen alone: 1.4 (1 ,0-2.0) estrogen and progestin. 2.3 (1.3-3.9) no significant association of ERT or PERT with invasive tumors duration of use: There was no significant association of use of ERT with duration of use. However, risk of in situ breast cancer rose with increasing duration of use, with users of 10 years or more having about twice the risk as non users (test for trend, p= 0.02). There was no clear pattern of risk associated with duration of use for PERT users, either for all cancers, in situ cancers or invasive tumors.	

[a]Unless otherwise specified, measured relationships relative risk of breast cancer in HRT
b 95 % confidence interval is given in parentheses.

KEY: c.i. = confidence interval; O.E. ratio = observed to expected ratio: OR = odds ratio; NS = not statistically significant; RR = relative risk

SOURCE: Office of Technology Assessment, 1995

TABLE F-4: HRT and Breast Cancer (Cohort Studies) with External Controls (Page 1 of 5)

Author	Description of study	Number of study subjects	Relationship of estrogen use to breast cancer risk	Relationship of duration of estrogen use to breast cancer risk[a,b]	Relationship of dose, recency, and latency of estrogen to breast cancer risk[a,b]
Burch (1 974)	Subjects were hysterectomized women on estrogen replacement therapy, followed for an average of 14.32 years. Expected number of deaths from U.S. Public Health Service cancer morbidity statistics.	1,000 hysterectomized women	Observed breast cancer cases. 33, expected. 23.7 observed breast cancer deaths: 6: expected: 7,85 No statistical analysis of the data was presented.		
Hoover (1976)	The medical records of all white women seen in one private practice in Louisville, KY, from 1939 to 1972, were reviewed. Expected rates for the general population were obtained from Second and Third National Cancer Surveys. Average age of women in the cohort was 49 years. Mean follow-up was 12 years.	1,891 women in cohort; 49 cases of breast cancer developed	RR 1.3 (1 .0-1 .7)	<5 yrs.: 0.9 (0,5-1 .5) 5-9 yrs.: 1.2 (0.6-2.0) 10-14 yrs.: 1.3 (0.6-2.4) 15+ yrs,: 2.0 (1,1 -3.4) Trend of greater risk with increased duration is statistically significant (p= 0.02). A finer breakdown of the follow-up duration after 10 years indicated that the excess becomes manifest after about 12 years of estrogen use. 10-12 yrs.: 1.2 (no c.i.) 13-16 yrs.: 1.9 17-24 yrs.: 2.0	"The increased risk associated with stronger medication and non-daily regimens are based on small numbers but are statistically significant. " 10+ years follow-up. 0.3 mg: 1.6 (0.9-2.7) 0.625 mg. 1.1 (0.5-2.0) >0,625 mg: 2.7(1 ,2-5.3) There was no statistically significant increase in breast cancer risk with less than 10 years followup.

TABLE F-4: HRT and Breast Cancer (Cohort Studies) with External Controls (Page 2 of 5)

Author	Description of study	Number of study subjects	Relationship of estrogen use to breast cancer risk	Relationship of duration of estrogen use to breast cancer risk [a,b]	Relationship of dose, recency, and latency of estrogen to breast cancer risk[a,b]
Hammond (1979)	Subject had been followed at least 5 years at Duke University Medical Center, Durham, NC, with diagnoses associated with a hypo-estrogenic state (e.g., premature ovarian failure or pituitary tumor). Information was gathered retrospectively from medical records, and in some cases from referring physicians, patients, or death certificates. Subjects were divided into two groups. those who never received estrogen and those who received estrogen for longer than 5 years. (Those estrogen users for 5 years or less were excluded.) The observed incidence of breast cancer was compared to age and race-specific incidence rates from the Third National Cancer Survey (southeast United States).	301 patients treated with estrogen and 309 untreated patients	Estrogen users. O.E. ratio 1.06 (O 3-2.7) for whites No breast cancers occurred in nonwhite estrogen users. nonusers of estrogen O.E. ratio 0.5 (O.1-1.5) for whites O.E. ratio 0.5 (0.0-2.9) for nonwhites		
Gambrell (1983)	Subjects were women from Wilford Hall USAF Medical Center in San Antonio, Texas who received various forms of hormonal therapy. Patients with a diagnosis of breast cancer between 1975 through 1981 were identified from a tumor registry. Expected values were obtained from the Third National Cancer Survey (1975) and the National Cancer Institute Surveillance, Epidemiology, End Result (SEER) data (1980). Information was gathered from mailed questionnaires, clinic and hospital records, and registries.	5,563 women; 53 cases of breast cancer	Estrogen plus progesterone O 3 (0.1-0.8) estrogen only. 0.7 (0.5-1.1) estrogen vaginal cream: 0.4 (0.2-1 .6) progesterone or androgen users. 0.7 (0.3-1.5) untreated women 1,4 (1 .1-1 9) This study was criticized for falling to control for confounding functions, including age,		

TABLE F-4: HRT and Breast Cancer (Cohort Studies) with External Controls (P

Author	Description of study	Number of study subjects	Relationship of estrogen use to breast cancer risk	Relationship of duration of estrogen use to breast cancer risk[a,b]	Relationship of dose, recency, and latency of estrogen to breast cancer risk[a,b]
Vakil (1983)	Incidence of breast cancer in a cohort of women, 32 to 62 years of age, receiving estrogen treatment for menopausal symptoms among the patients of 20 gynecologists in the metropolitan Toronto area was compared to two control groups: the age-specific breast cancer incidence rates of the female populations of Ontario and of Saskatchewan. Estrogen therapy was begun between 1960 and 1970 and subjects were followed up to 17 years. Information was gathered from gynecologists and cancer and death registries.	1,483 menopausal women	Standard mortality ratio for breast cancer. 0.48 (p < 0,01) compared with Ontario controls, 0.45 (p< 0.01) compared with Saskatchewan controls standard incidence ratio of breast cancer. 0.62 (p < 0,01) compared with Ontario controls; 0.70 (p < 0.01) compared with Saskatchewan controls		
Hunt (1987)	Subjects were women receiving hormonal replacement therapy, recruited from 21 menopause clinics around Britain. Subjects were followed from 1978 to 1982. Most women were 45 to 54 years of age at time of recruitment. Subjects were recruited both retrospectively and prospectively. Expected numbers were obtained from cancer registry roles. All patients were interviewed at study initiation. Deaths were reported from central registries.	*4,544* women; 503 cases of breast cancer	O.E. ratio breast cancer incidence 1.59 (1 18-2,10) hysterectomy only O.E. ratio 3.08 hysterectomy and oophorectomy O.E. ratio 166 natural menopause. O.E ratio 1.19	There was no significant increase in incidence with increasing duration of estrogen use	Interval since first use of HRT: O-4 years. O.E. ratio 1.40 (0.85-2.46) 5-9 years. O.E. ratio 1.45 (0.88-2.24) 10+ years O.E. ratio 3.07 (1 .47-5.64) There was evidence of a trend in ratio with interval since first use (test for trend. p = 0.08).

TABLE F-4: HRT and Breast Cancer (Cohort Studies) with External Controls (Page 4 of 5)

Author	Description of study	Number of study subjects	Relationship of estrogen use to breast cancer risk	Relationship of duration of estrogen use to breast cancer risk[a,b]	Relationship of dose, recency, and latency of estrogen to breast cancer risk[a,b]
Dupont 1989)	Study subjects were women who underwent biopsy for benign breast disease at three Nashville hospitals between 1950 and 1968. Median duration of follow-up is 17 years. Reference population consisted of white women from Atlanta who participated in the Third National Cancer Survey. Ninety percent of study subjects were either postmenopausal or were at least 50 years old by the end of their follow-up. Information was gathered from clinic and hospital records, questionnaires, and death certificates.	10,366 biopsies evaluated; follow-up information obtained on 3,303 women; 35 cases of breast cancer	RR 0.98 (no c.i. reported)	Breast cancer risk was not elevated in women who took estrogens for more than five years."	
Hunt (1990)	Breast cancer death rates in women recruited from 21 menopause clinics in Britain and who had taken at least one year's continuous HRT at the time of recruitment to the study were compared with age-specific death rates in the female population in England and Wales. Subjects were recruited both retrospectively and prospectively. Subjects were followed from 1978 to December 1988. Most women were age 45 to 54 years of age at time of recruitment. All subjects were interviewed at study initiation. Deaths were reported from central registries.	4,544 women in cohort; 31 breast cancer deaths	Breast cancer death: all women: O.E. ratio 1.00 (0.55-1.45) hysterectomy only: O.E. ratio 0.74 hysterectomy and oophorectomy: O.E. ratio 0.82 natural menopause: O.E. ratio 0.74		Deaths from breast cancer by years since first exposure (O.E. ratio): 0-4 years: 0.38 (0.00-1.07) 5-9 years: 0.74 (0.27-1.21) 10+ years: 0.97 (0.47-1.47) (test for trend: NS)

TABLE F-4: HRT and Breast Cancer (Cohort Studies) with External Controls (Page 5 of 5)

Author	Description of study	Number of study subjects	Relationship of estrogen use to breast cancer risk	Relationship of duration of estrogen use to breast cancer risk[a,b]	Relationship of dose, recency, and latency of estrogen to breast cancer risk[a,b]
Risch (1 994)	Subjects were women ages 43 to 49 years of age in 1976, resident in Saskatchewan, Canada, who were identified for the master file of the government health Insurance plan that covers virtually all residents of the province. These women's health plan registration number was used to obtain their prescription records form the plan's pharmacy database for the period from January 1976 to June 1987, The women's health plan registration number allowed the investigators to Iink the women's pharmacy records to the Saskatchewan Provincial Cancer Registry. Thirty-one percent of the cohort used in opposed estrogens (mostly conjugated estrogens), 2,07 percent used opposed estrogens, Estrogen use was defined as use of 3.5 years or more.	32,790 women(742 breast cancer cases)	Unopposed estrogen 1,33 (1.1 1-1 ,59) both opposed and unopposed estrogen 1.10 (O *35-O 42)* No breast cancer cases occurred among the 171 subjects who used opposed estrogens progestins (both alone or combined with estrogen) 0,93 (0.51 -1 68)	For unopposed estrogen, risk increased by 7 percent for each 252 tablets prescribed (approximately I year of use) (RR 1072 (1 02-1.13) For opposed estrogens, there was no significant increase in risk for each 252 tablets prescribed (RR 1,211 (0.72-2.05). For unopposed progestins, there was no significant increase in risk for each 84 tablets prescribed (equal to seven tablets per month for 12 months) (RR 1,0003 (O 80-1 25)).	Unopposed estrogens, 1 to 126 tablets/yr. 1,039 (O 78-1 38) 127-378 tablets/yr 1,161 (0,83-1 63) 379-756 tablets/yr 1,041 (0,66-1 63) >757 tablets/yr 1.498 (1 ,05-2,13)

[a]Unless otherwise specified, measured relationships relative risk of breast cancer in HRT
b 95% confidence Interval is given in parentheses

KEY: c.i. = confidence internal; NS = not statistically **significant; O.E.** ratio = **observed to** expected ratio; O.R. = odd ratio; RR = relative risk

SOURCE: Office of Technology Assessment, 1995

Appendix G: Evidence on HRT and Endometrial Cancer

G

Endometrial cancer, the most common gynecologic cancer, occurs in about one woman out of 1,000 in the population each year (15). An average 50-year-old white woman has a 2.6 percent lifetime risk of endometrial cancer (l). And about eight out of every 100 women diagnosed with endometrial cancer die of this disease (l). Evidence that estrogen replacement therapy increases the risk of endometrial cancer is well established and is consistent with a variety of observations.

The relationship of endometrial cancer with use of estrogen replacement therapy is consistent with trends in the incidence of endometrial cancer. In the United States, there was a dramatic increase in prescriptions for estrogen replacement therapy between the mid- 1960s and the early 1970s (47). Estrogen was usually prescribed alone, without a progestin, and was given for three weeks out of a four-week cycle. A rise in incidence of endometrial cancer coincided with this increase in prescriptions for estrogen. By 1976, the first case-control studies were published that revealed significant increases in risk of endometrial cancer in estrogen users compared with nonusers (57,73, 92). After these reports, sales of estrogen replacement therapy began to drop, as did endometrial cancer rates (47). Since 1980, prescriptions for estrogen replacement therapy have been on the rebound as physicians have been prescribing progestins in sequence with estrogens to prevent estrogen from inducing endometrial hyperplasia (19,47).

Obesity and other conditions associated with a high level of endogenous estrogens are associated with an increased risk of endometrial cancer, so it is not surprising that estrogen replacement therapy also increases the risk of endometrial cancer (7).

The increase in endometrial cancer with estrogen replacement therapy is also physiologically plausible, and is consistent with observations about the relationship of estrogen to the endometrium. Estrogen is a growth hormone for the endometrial tissue lining the inside of the uterus. In premenopausal women, estrogen levels begin to rise at the beginning of the monthly menstrual cycle, and progesterone levels increase near the end of the cycle, causing the endometrial tissue to mature. In the absence of implantation of a fertilized egg into the endometrium, estrogen and progesterone levels fall and the endometrial tissue is sloughed off, resulting in menstruation.

If estrogen stimulation continues unopposed by progesterone, the endometrium continues to grow, producing hyperplasia, or overgrowth of the

endometrium (19). Hyperplasia has been shown to advance to carcinoma in situ, and eventually to endometrial cancer (31,52,63). This progression has been observed in patients with diseases characterized by excessive unopposed estrogen secretion, such as Stein-Leventhal Syndrome (74), estrogen-producing tumors (32), and certain types of infertility (69). Progestins have been shown to produce maturation of estrogen-primed endometrium and regression of hyperplastic tissue to normal endometrium (79). It has even led to regression of some well-differentiated carcinomas in some patients (24,67).

Numerous case-control and cohort studies have documented an increase in endometrial cancer with use of estrogens. These are presented in tables G-1 to G-4 at the end of this appendix.

Up to 20-fold increases in risk of endometrial cancer have been detected in case-control studies of estrogen replacement therapy. (See tables G-1 and G-2.) Among case-control studies, relative risks are generally lower in hospital-based case-control studies that use as controls women with gynecologic problems, probably because uterine bleeding is one of the most common gynecologic problems and estrogen commonly causes this symptom (28). Relative risks are generally higher in population-based case-control studies and hospital-based case-control studies that use as controls women without gynecologic problems, in part because surveillance for endometrial cancer is increased among women taking estrogen (28).

DURATION AND DOSE OF ESTROGEN

Studies of the relationship of endometrial cancer to duration of estrogen replacement therapy indicate that significant increases in risk of endometrial cancer can be detected in as little as six months to one year after initiation of estrogen replacement therapy (4,58,72,75,92). Epidemiologic studies have shown that the risk of endometrial cancer increases with increased duration of use. (See tables G-1 to G-4.) For 10 or fewer years of use, the risk ranges from no significant increase to a 36-fold increase in risk. For more than 10 years of use, the increase in risk has been estimated to be as little as 2.6 to as great as 63.

The risk of endometrial cancer has been shown to be related to dose of estrogen. (See tables G-1 to G-4.) Hence, the minimum effective dose to maintain bone mineral density and to relieve postmenopausal symptoms is commonly prescribed. (See appendix E.)

RECENCY OF USE OF ESTROGEN

The risk of endometrial cancer decreases after cessation of therapy. Some studies have reported that risks of endometrial cancer returned to levels of nonusers after only six months to two years (40, 57), while others have found the increase in risk to persist for up to 15 years after estrogen replacement therapy is stopped (8,62,70,72). The data comparing the trends of estrogen prescription volume with endometrial cancer incidence are more consistent with a short time interval between cessation of estrogen replacement therapy and decline in endometrial cancer risk (5).

STAGE AND GRADE OF ENDOMETRIAL CANCER

Endometrial cancer arising in estrogen users is of lower stage and grade and much less likely to result in death than endometrial cancer arising in nonusers of estrogen. A number of case-control studies have consistently found a lower stage and grade of endometrial cancer in estrogen users. (See table G-3.) Virtually all endometrial cancers in estrogen users are diagnosed before they have spread beyond the uterus. In cases where endometrial cancer has not spread beyond the uterus, hysterectomy is usually curative. The survival among estrogen users diagnosed with endometrial cancer is favorable (12). Barrett-Connor reported that women not on estrogen survive less well than women with endometrial cancer taking estrogen (6). Furthermore, there was little evidence that mortality from endometrial cancer increased during the period of rising incidence of the disease from estrogen use in the population (47).

However, some users of estrogen replacement therapy do develop cancers that have spread beyond the uterus (Stage III and Stage IV) (23, 70, 72), and some estrogen users die of this complication (18,57,62).

There are several factors that may account for this relatively favorable prognosis. First, the lower stage and grade of endometrial cancer in estrogen users may be due to detection bias. Estrogen users are closely monitored with endometrial biopsies annually and at times of irregular bleeding. Vaginal bleeding is an early symptom of endometrial cancer, and women taking estrogen replacement therapy may bleed earlier and be biopsied earlier than women receiving less regular medical care (7,56). The favorable stage and grade may also be due in part to case ascertainment — the detection of occult cancers in the endometrium of users who bleed because they are taking estrogen (38). The apparently favorable survival experience of user cases is also likely due in part to patients with estrogen-induced benign hyperplasia mislabeled as cases (56). Bias may also be introduced by a greater likelihood of estrogen treatment in women who have menopausal problems associated with unsuspected cancer or a greater likelihood of cancer (56).

The lower stage and grade of estrogen-induced tumors may be because these tumors are more benign than tumors that arise in the absence of estrogen. Estrogen-induced endometrial cancers may be better differentiated and slower growing than endometrial cancers that arise in the absence of inducement by exogenous estrogen.

Estrogen-induced irregular bleeding, hyperplasia, and localized cancers of the endometrium result in an increased prevalence of hysterectomy among estrogen users (20). Thus, even though the endometrial bleeding, hyperplasia, and cancers associated with estrogen use do not substantially increase mortality, they do contribute to medical costs associated with estrogen replacement therapy **(15).**

Weiss and colleagues were among the first to suggest that endometrial cancers that arise in women taking estrogen replacement are on average less aggressive than those that arise in women who have not taken estrogen replacement (82). The author reviewed five case-control studies examining the association between prior postmenopausal estrogen use and endometrial cancer prognosis. They found that, although estrogen use is associated with an increased risk of endometrial cancer, that association tended to weaken when only invasive and high-grade tumors are considered. The authors explained that one possible reason for this finding was that tumors that arise in the presence of exogenous estrogens are on average less aggressive than those that arise in their absence. Another possible explanation, they noted, was detection bias, that endometrial cancer in estrogen users may be detected earlier than in nonusers of estrogen. This may be because estrogen users may tend to seek care more promptly than nonusers, their access to medical care may be greater, or the physicians of estrogens may detect endometrial cancers early because they are particularly wary of the development of these cancers in their patients on estrogen.

A third possible explanation, according to the authors, is overdiagnosis of endometrial cancer in estrogen users. Because the histological criteria for separating the more advanced cases of endometrial hyperplasia are ambiguous, some cases of estrogen-related advanced hyperplasia are being incorrectly labeled as early endometrial cancer, giving rise to a false association of estrogen use with low-grade, low-stage cancers.

Deligdisch and Holinka have provided additional evidence that patients known to be at increased risk of endometrial cancer due to exposure to estrogen are likely to develop better differentiated and less aggressive forms of cancer (16). The researchers examined the cellular characteristics of the tumors of 95 patients with Stage I endometrial cancer. Noting that endometrial hyperplasia is excessive growth of endometrial tissue caused by estrogen stimulation, they found that endometrial cancers with hyperplasia were better differentiated and less invasive than endometrial cancers without hyperplasia.

ESTROGEN USE AND SURVIVAL FROM ENDOMETRIAL CANCER

Epidemiologic studies have consistently found that, among postmenopausal women diagnosed with endometrial cancer, estrogen users have markedly better survival than never users of estrogen.

Robboy et al. concluded that survival differences between estrogen users and nonusers was due to differences in grade of tumor at diagnosis (68). The authors identified 274 women treated for endometrial cancer at the Massachusetts General Hospital between 1940 and 1971. Pathological specimens for each woman were examined to confirm the diagnosis of endometrial cancer. Hospital and clinic records were available for 190 of these women, and were reviewed for a history of postmenopausal estrogen use. They found that 85 percent of the 274 patients with endometrial cancer were stage I at diagnosis, and 7 percent were stage II, with no significant difference in stage at diagnosis between estrogen users and nonusers. However, the tumors that developed in estrogen users were significantly more differentiated than those that developed in nonusers (p less than 0.05). Five- and 10-year survival was also significantly better in users than in nonusers, but survival in users and nonusers was not significantly different once adjusted for differences in grade of tumor.

The authors did not rule out that their findings could be explained by earlier detection in estrogen users because of better endometrial cancer surveillance. This explanation was supported by the fact that the average age of estrogen users at diagnosis was four years less than nonusers (56 versus 60 years of age, p less than 0.02).

Elwood et al. concluded that survival differences between estrogen users and nonusers is almost entirely due to differences in the stage and grade of endometrial cancers at diagnosis (1 8). Elwood et al. studied 494 women seen at a Vancouver clinic between 1968 and 1972 for treatment of newly diagnosed endometrial cancer. All patients were followed until death or to 1975. Information on estrogen use was based on both the patient's history and the response of the family physician to a letter requesting more detailed information. The investigators compared the stage and grade of endometrial cancer in ever users of CEE to never users of postmenopausal estrogens. Only 8 percent of CEE users had Stage H or III cancers at diagnosis, compared with 16 percent of nonusers. And 43 percent of tumors in CEE users were well differentiated, compared with 29 percent of nonusers.

The 5-year survival rate, after adjustment for age, was 94.2 percent in ever users of CEE and was 81.3 percent in nonusers, a difference that was highly significant ($p = 0.001$). When differences in stage were taken into account, survival was not significantly different between the two groups.

Collins et al. studied endometrial cancer stage, grade, and survival in 860 women referred to a London, Ontario cancer clinic between 1967 and 1976 (13). Information on prior estrogen use was obtained through a questionnaire. About one third of the patients had a history of estrogen use, defined as use of estrogen for 6 months or more before diagnosis.

At all stages of endometrial cancer, estrogen users had a significantly greater 5-year survival than nonusers. The researchers found that, after adjusting for a number of risk factors for mortality, endometrial cancer patients with no history of prior estrogen use had a 5.4 times greater risk of death from cancer than endometrial cancer patients with a history of prior estrogen use.

The authors posited that endometrial cancer patients with a history of estrogen use had higher survival rates because cancers associated with prior estrogen use are less aggressive tumors. The authors, however, did not rule out the possibility that selection or surveillance bias may have confounded their findings.

In a study of 379 white women ages 50 to 74 from King County, Washington, with newly diagnosed endometrial cancer, Chu and colleagues concluded that although the use of postmenopausal estrogen leads to an increased risk of endometrial cancer, there is no increased risk of endometrial cancer death in postmenopausal estrogen users (12). The authors obtained information on

cases of endometrial cancer diagnosed between January 1975 and April 1976 from the Cancer Surveillance Center, a population-based registry serving western Washington State. Additional information was obtained from interviews of the patient's physician. Information on estrogen use, medical and reproductive history, and risk factors for endometrial cancer was obtained by interviewing the patient; for the 12 percent of study participants who could not be interviewed, this information was obtained by reviewing the medical records of primary care physicians. Fully 98 percent of estrogen users (defined as use of estrogen for one or more years after menopause) had tumors stage O or I at diagnosis, compared with 88 percent of nonusers. Only 2 percent of estrogen users had stage II or III cancers at diagnosis, compared to 12 percent in nonusers, a difference that was statistically significant.

Estrogen users with endometrial cancer had a small but significantly better four-year survival rate than women of the same age in the general population, as calculated from Washington state life tables for white women (relative survival ratio 1.05 (1.04-1.06)). Estrogen users with endometrial cancer also had a significantly better four-year survival than nonusers with endometrial cancer, the latter group having a relative survival ratio of 0.89 (0.80-0.99) compared with women of the same age.

The authors stated that the possibility that these results were due to self selection or detection bias could not be ruled out. They also mentioned that other factors that may confound the interpretation of their results include differences in follow-up between estrogen users and nonusers, differences in cancer therapy between estrogen users and nonusers. They also noted that the interpretation of results may be limited by the relatively short (four-year) follow-up period.

ESTROGEN/PROGESTIN REPLACEMENT THERAPY

Because even a relatively benign cancer is an unacceptable complication, most physicians add a progestin to suppress endometrial hyperplasia (16). There is substantial evidence that women who take progestins with estrogen are at no increased risk of developing endometrial cancer compared with postmenopausal women who do not take estrogen.

Until recently, only large-scale cross-sectional studies were available on the effect of combined estrogen and progestin therapy on endometrial cancer risk, and these studies showed that the combination reduced the incidence of endometrial cancer to below that of an untreated population (25). A number of prospective studies have shown that the incidence of endometrial cancer is increased with unopposed estrogen replacement therapy, but not with combined estrogen and progestin therapy (25, 64).

Persson et al. examined the incidence of endometrial cancer in hormone replacement therapy (HRT) in the Uppsala health care region, which serves one-sixth of the population of Sweden (64). Using the region's prescription database, he was able to identify 23,244 women over age 35 who filled one or more prescriptions for HRT between April 1977 and March 1980. Women from the cohort who developed endometrial cancer were identified from the region's cancer registry. Information on lifetime exposures to estrogen and progestin, compliance, and sociodemographic data were obtained on 735 randomly selected members of the cohort. Comparison was made to women in the general background population.

A relatively high proportion of the HRT users in this cohort were receiving progestin and estrogen replacement therapy (PERT), allowing comparison to be made with estrogen replacement therapy (ERT) (64). The investigators found that, while users of ERT has a significantly increased risk of endometrial cancer (relative risk 1.8 (95 percent confidence interval 1.1 to 3.2) after exposure to any estrogen for 6 years), users of PERT were at no increased risk (relative risk 0.9 (95 percent confidence interval 0.4 to 2.0)).

However, for some of the less androgenic progestins (such as medroxyprogesterone acetate (Provera), the most commonly used progestin in the United States), and in the regimens and lower

doses commonly used today, there are insufficient studies with endometrial cancer as an endpoint; most studies of efficacy look at an intermediate endpoint, such as reversal of endometrial hyperplasia. Medroxyprogesterone acetate, in a dose of 10 mg for 12 days, is the least androgenic regimen that has been best documented to prevent hyperplasia (63,85).

Although courses of medroxyprogesterone acetate of fewer than 12 days have been shown to reduce the incidence of estrogen-induced endometrial hyperplasia (86), the minimum duration to reduce the incidence to zero is 12 days per month (64,78,87).

Some clinicians prefer a lower dose, 2.5 or 5 mg, of medroxyprogesterone acetate. These smaller doses are often given concurrently with estrogen throughout the month (7,84). A continuous low-dose regimen avoids the withdrawal bleeding of cyclic progestin, which may lead to poor compliance. In addition, these lower doses are less likely to induce premenstrual-type symptoms associated with progestins Long-term data on the ability of continuous low-dose progestin to protect the endometrium overtime is limited (85). Additional data is also needed on the effects of these treatments on lipids, lipoproteins, and other metabolic parameters (11).

One recent case-control study provides evidence that menopausal women taking estrogen replacement therapy can significantly reduce their risk of endometrial cancer if they also take medroxyprogesterone (45). The study examined women between the ages of 50 and 64 who were treated from 1979 to 1989 at Group Health, a Seattle, Washington health maintenance organization. Researchers identified 172 cases of endometrial cancer and compared use of hormones in these women with that of 1,720 women who did not have cancer. Users of combined therapy used medroxyprogesterone acetate, 10 mg per day, most for 10 days each month.

Current users of estrogen alone had a relative risk of endometrial cancer of 6.5 (95 percent confidence interval 3.1 to 13.3), whereas current users of estrogen and progesterone had a relative risk of 1.9 (95 percent confidence interval 0.4 to 8.7). Past users of estrogen alone or estrogen and progestin had no increased risk of endometrial cancer. The study found that users of estrogens for three to four years had a relative risk of 1.9 (95 percent confidence interval 0.4 to 8.7), and that users of five years or more had a relative risk of 22 (95 percent confidence interval 1.5 to 24.1). Users of estrogen and progestin for more than three years had a relative risk of 1.3 (95 percent confidence interval 0.5 to 3.4). The researchers concluded that there does not appear to be any substantial increase in risk associated with combined use with increasing duration of therapy. The researchers cautioned, however, that there were relatively few women who used combined therapy for more than five years.

A number of clinical trials have demonstrated that the sequential or continuous addition of a progestin reduces the incidence of or eliminates endometrial hyperplasia, thought to be a precursor to endometrial cancer. Woodruff and Pikar examined the incidence of hyperplasia in a one-year, randomized clinical trial of conjugated estrogens (Premarin) and medroxyprogesterone acetate (Provera) in 1,724 postmenopausal women (91). The subjects were divided into five groups: two groups received continuous estrogen/progestin regimens, two groups received sequential estrogen/progestin regimens, and one group received unopposed estrogen regimen.[1] They found that, while endometrial hyperplasia developed in 20 percent of women on Premarin alone, hyperplasia

1 The regimens examined were as follows: (1)0.625 mg Premarin plus 2.5 mg Provera daily; (2) 0.625 mg Premarin plus 5 mg Provera daily; (3) 0.625 mg Premarin daily plus 5 mg Provera for 14 days per month; (4) 0.625 mg Premarin plus 10 mg Provera for 14 days per month; and (5) 0.625 mg Premarin daily unopposed by progestin (Woodruff, 1994).

developed in one percent or less of women in the four Premarin/Provera groups (91).[2]

Other trials of sequential or continuous regimens using other estrogens and progestins have demonstrated less hyperplasia in PERT users than in users of estrogen alone (21,90).

Although the incidence of endometrial cancer is reduced in estrogen-progestin users, the risk of endometrial cancer is not eliminated completely. One group of investigators reported on 25 postmenopausal women who developed endometrial cancers while taking PERT for one or more years (59). Twenty-three (98 percent) of the women had cancers limited to the uterus, but two had disease extending beyond the uterus. All of the women were alive and disease free after a median follow-up of 26 months. The endometrial cancers that did occur among PERT users were usually associated with regimens that had inadequate doses of progestins.

IMPLICATIONS FOR OTA'S COST EFFECTIVENESS MODEL

The evidence is strong that endometrial cancer risks begin to rise soon after the initiation of ERT. Following the weight of the evidence presented in tables G-1 and G-2, OTA assumed that the relative risk of endometrial cancer during the first nine years of ERT would be 2.5 and in subsequent years would rise to 7.0. The sensitivity of results to changes in these assumptions was also tested. For the case most favorable to ERT, OTA assumed that relative risk of endometrial cancer is 1 for the first nine years of therapy and rises to 2.0 during the 10th and subsequent years of ERT. This best case is based on the assumption that the apparent increased risk of endometrial cancer in ERT users is largely due to surveillance bias. In the worst case, the relative risk would be 7.5 in the first nine years of ERT and 15.0 thereafter. This estimate is based on epidemiological studies that detected the highest risks of endometrial cancer in HRT users.

In a recent metaanalysis, Grady et al. estimated a risk of endometrial cancer in ERT users that was intermediate between OTA's base case and worst case estimates (28). They concluded that the risk of endometrial cancer increased with prolonged duration of ERT use, from a relative risk of 1.4(95 percent confidence interval 1.0 to 1.8) for less than one year of use, 2.8 (95 percent confidence interval 2.3 to 3.5) for two to five years of use, 5.9 (95 percent confidence interval 4.7 to 7.5) for six to 10 years of use, and 9.5 (95 percent confidence interval 7.4 to 12.3) for more than 10 years of use (28).[3]

For PERT users, OTA assumed that there would be no increase in endometrial cancer risk over that of the baseline population. This is consistent with the estimates of endometrial cancer risk from the metaanalysis by Grady and colleagues, who found that case-control studies estimated a slightly increased risk of endometrial cancer in PERT users (relative risk 1.8), whereas the few cohort studies of PERT users have estimated a slightly decreased risk of endometrial cancer (relative risk 0.4) (28).

In modeling the impact of HRT on endometrial cancer, OTA made a number of simplifying assumptions. In the case of ERT, OTA assumed that the relative risk of endometrial cancer would subside to that of the baseline population in the year following cessation of HRT. This assumption is consistent with observations that the risk of endometrial cancer drops rapidly after discontinuing estrogen use. There are, however, a number of studies that have been able to detect relatively small elevations in risk of endometrial cancer that persist several years after cessation of therapy. Grady et al. estimated a relative risk of endometrial cancer of 2.3 (95 percent confidence intervals 1.8 to 3.1) five or more years after discontinuation of long-term ERT use (28).

OTA assumed that endometrial cancers in HRT users would be early stage and grade, and would

2 Although the incidence in endometrial hyperplasia did not differ significantly among the Premarin/Provera groups, none of the women who received the sequential or continuous regimens with the highest dosages of progestins developed endometrial hyperplasia (91).

3 An earlier metaanalysis by Grady and colleagues estimated a relative risk of 8 in long-term estrogen users (28).

be cured by hysterectomy. OTA also assumed, for simplicity, that there would be no endometrial cancer deaths in HRT users. The metaanalysis by Grady et al. estimated that ERT is related to a large increase in risk of early stage cancers (relative risk 4.2 (95 percent confidence interval 3.1 to 5.7) for Stage O and 1 cancers) (28). They found a trend toward later stage endometrial cancers in ERT users that did not reach statistical significance (relative risk 1.4 (95 percent confidence interval 0.8 to 2.4) for Stage 2 to 4 cancers).

Observational studies have been unable to detect a significantly increased risk of endometrial cancer death in ERT users (20,49,62,65). This may be due in part to the small number of endometrial cancer deaths in these studies. In a metaanaly - sis, Grady and colleagues were able to use pooled data from these studies to detect a trend toward increased endometrial cancer deaths in ERT users that failed to reach statistical significance (relative risk 2.7 (95 percent confidence interval 0.9 to 8.0)) (28). Because endometrial cancer is less common than breast cancer, hip fracture, or heart disease, and because there are relatively small numbers of invasive endometrial cancers and deaths due to HRT-induced endometrial cancer, OTA's simplifying assumptions about endometrial cancer stage and endometrial cancer deaths in ERT users should not have a substantial impact on the results of OTA's analysis.

OTA also assumed that women diagnosed with endometrial cancer would remain off hormonal replacement therapy. It was previously thought that HRT could induce the growth of any residual endometrial cancer cells, and thereby increase the risk of recurrence. There is a growing consensus, however, that a history of endometrial cancer is not a contraindication to continuing HRT, at least with respect to women who have had hysterectomies for tumors that have not spread beyond the uterus (3,14,60). It is doubtful, however, that most women would be willing to resume HRT after having had endometrial cancer.

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TABLE G-1: HRT and Endometrial Carcinoma: Hospital-Based Case Control Studies (Page 1 of 17)

Author	Description of cases and controls	Number of cases and controls	Relationship of endometrial cancer to estrogen use[a,b]	Relationship of endometrial cancer to duration of estrogen use[a,b]	Relationship of endometrial cancer to dose of estrogen[a,b]	Relationship of endometrial cancer to recency of estrogen use [a,b]
Smith 1975)	Cases were patients from Mason Clinic, Virginia Mason Hospital, Seattle, WA, and University of Washington Medical School Hospital who were 48 years of age or older with diagnosis of endometrial carcinoma made between 1960-1972 after curettage or hysterectomy. Matched controls were selected from patients with other gynecologic neoplasms at the same institutions. Controls were matched with cases for age at diagnosis and year of diagnosis. Cases and controls were selected from regional tumor registry. Information was gathered from medical records	317 cases (48% estrogen users); 317 controls (17% estrogen users)	Unadjusted relative risk 4.5 (no confidence intervals provided) Relative risk 7.5, adjusted for year and age at diagnosis			

TABLE G-1: HRT and Endometrial Carcinoma: Hospital-Based Case Control Studies (Page 2 of 17)

Author	Description of cases and controls	Number of cases and controls	Relationship of endometrial cancer to estrogen use[a,b]	Relationship of endometrial cancer to duration of estrogen use[a,b]	Relationship of endometrial cancer to dose of estrogen[a,b]	Relationship of endometrial cancer to recency of estrogen use [a,b]
Gray (1977)	Cases were endometrial cancer patients seen in one private practice between 1947 and 1976. One control was chosen for each case from among those patients who had a hysterectomy for a benign condition performed in the same year in which the patient with endometrial cancer was diagnosed. Once the year was determined, the specific control was chosen from all those available matched as closely as possible to the case on the basis of age and parity. Average age of cases was 56.5 years, controls 56.0 years. Information was obtained from medical records.	205 cases (27% estrogen users); 205 controls (15% estrogen users)	All estrogens: 2.1 (1.2-3.5) Conjugated estrogens: 3.1 (1.5-6.8) Systemic estrogens: 2.6 (1.5-4.6) No evidence of increased risk associated with vaginal estrogenic preparations: 0.7 (0.1-3.6)	0-4 yrs.: 1.2 (0.4-3.5) 5-9 yrs.: 4.1 (0.8-28.4) 10+ yrs.: 11.6 (1.5-242.7)	♀.3 mg: 4.1 (0.8-40.♀ ♀.625 mg: 1.8 (0.7-4.9) 1.25 mg: 12.7 (1.8-552.3)	
Hoogerland (1978)	Cases were all patients treated for invasive cancer of the endometrium in the Wisconsin Clinical Cancer Center from 1960 to 1974. Controls were hospital patients with a different gynecological malignancy, matched for age and date of diagnosis. Information was gathered from medical records.	587 cases (18.4% estrogen users); 587 controls (9.2% users)	2.2 (1.6-3.2)	1-6 mos.: 1.2 7-12 mos.: 1.8 1-3 yrs.: 3.2 3-5 yrs.: 3.9 5-10 yrs.: 3.4 10+ yrs.: 6.7 (No tests of statistical significance were conducted because of the small numbers of cases involved.)		

TABLE G-1: HRT and Endometrial Carcinoma: Hospital-Based Case Control Studies (Page 3 of 17)

Author	Description of cases and controls	Number of cases and controls	Relationship of endometrial cancer to estrogen use[a,b]	Relationship of endometrial cancer to duration of estrogen use[a,b]	Relationship of endometrial cancer to dose of estrogen[a,b]	Relationship of endometrial cancer to recency of estrogen use [a,b]
Horowitz (1978)	Cases were women, mean age 61 years, with endometrial cancer listed in the Yale Tumor Registry between July 1, 1974 and June 30, 1976; cases had to have endometrial carcinoma of Grade I or higher (Stage 0 "in situ" carcinoma was excluded). Controls were women with other gynecologic cancers listed in the Yale Tumor Registry between July 1, 1974 and June 30, 1976, matched for age and race to cases. Information on HRT use was obtained from hospital and clinic records.	119 cases (29% estrogen users); 119 controls (3% estrogen users)	Odds ratio 11.98 (4.02-47.73)	< 3.5 yrs.: odds ratio 0.8 (0.4-1.7) compared with gynecology controls; odds radio 0.7 (0.4-1.3) compared with community controls		
Horowitz (1978) (alternate method)	Cases were women, mean age 62 years, with endometrial cancer who underwent dilation and curettage or hysterectomy between January 1, 1974 and June 30, 1976. Controls were women with diagnoses other than uterine cancer matched for age and race to cases. Information on HRT use was obtained from hospital and clinic records.	149 cases (30% users); 149 controls (15% estrogen users)	Odds ratio (alternative method) 2.3 (1.26-4.25)			

TABLE G-1: HRT and Endometrial Carcinoma: Hospital-Based Case Control Studies (Page 4 of 17)

Author	Description of cases and controls	Number of cases and controls	Relationship of endometrial cancer to estrogen use[a,b]	Relationship of endometrial cancer to duration of estrogen use[a,b]	Relationship of endometrial cancer to dose of estrogen[a,b]	Relationship of endometrial cancer to recency of estrogen use[a,b]
Wigle (1 978)	Cases were women aged 55 to 74 years with histologically confirmed endometrial cancer who first attended an Alberta, Canada cancer clinic during the period 1971 to 1973. Controls were women aged 55 to 74 years who attended the cancer clinic for any primary cancer other than breast, cervix, uterus, ovary, or other female genital organs. Information on HRT use and risk factors was gathered by questionnaire.	202 cases (47.2% estrogen users), 1,243 controls (26.3% estrogen users)	Any use, 2,2 (p< 0.01) Estrogen users was defined as users of hormonal replacement therapy or oral contraceptives.	1-4 years 1.8 (p< o 05) > 5 years 5,2 (p< 0,05)		Current use. 2.7 (p < 0,01) Past use. 2.0 (p< 0,01)
Jick (1979)	Cases were women 50 to 64 years of age who were members of Group Health Cooperative of Puget Sound, Seattle, Washington, who were diagnosed with endometrial cancer from January 1972 to June 1977. Controls were members of the same age that were hospitalized for other conditions at the same age as cases. Information was obtained from telephone interviews and clinic records,	67 cases (89.6% estrogen users); 74 controls (43.2% estrogen users)	Ever use: relative risk 11.2 (4,2 -21 .1)	Duration of use: O-4 years: 3.0 (0.5-14.9) 5-8 years: 36.0 (5.6-300.9) 9-12 years 63.0 (10,4-502.9) 13 years. 21.0 (4.6-107.9) Relative risk estimates were calculated by Grady (1995) from published crude data.	Dose: 0.3 mg CEE: 4.3 (1 .2-15 .6) 0.625 mg CEE: 7.1 (2,8-1 7.6) 1.25 mg CEE: (8.4 (2,0-36.5)	

TABLE G-1: HRT and Endometrial Carcinoma: Hospital-Based Case Control Studies (Page 5 of 17)

Author	Description of cases and controls	Number of cases and controls	Relationship of endometrial cancer to estrogen us&[b]	Relationship of endometrial cancer to duration of estrogen use [a,b]	Relationship of endometrial cancer to dose of estrogen [a,b]	Relationship of endometrial cancer to recency of estrogen use [a,b]
Antunes (1979)	Cases were all patients with endometrial cancer admitted to six of the 24 hospitals in the Greater Baltimore area from 1973 to February 1977. Cases were ascertained from hospital tumor registries, admissions records, and pathology records. Controls were female patients who were matched with cases for hospital, race, age, and date of admission, One set of controls were taken from hospital services other than gynecology, obstetrics, and psychiatry services. A second set of controls was taken from the gynecology service, Information was gathered through personal interviews, medical records, and pathologenic specimens.	451 cases (20% estrogen users); 446 controls from other services; 442 gynecology controls	Unadjusted relative risk 6.0 (3.7-9.7) compared with hospital controls Unadjusted relative risk 2.1 (1.5-NA) compared with controls from gynecology service Adjusted relative risk 5.5 (2.3-12.9) compared with " hospital controls Adjusted relative risk 2.4 (1 ,5-3.7) compared with gynecology controls	None: 1.0 <1 yr.: 2.2 (0,9-5,5) 1-5 yrs.: 2.9 (1 ,3-6.7) >5 yrs.: 15 (4,9-45)	<1 mg: 3,5 (1 ,6-7,6) 1-2 mg: 7,1 (2,8-18) >2 mg.: 3.7 (0,8-16)	

TABLE G-1: HRT and Endometrial Carcinoma: Hospital-Based Case Control Studies (Page 6 of 17)

Author	Description of cases and controls	Number of cases and controls	Relationship of endometrial cancer to estrogen use [a,b]	Relationship of endometrial cancer to duration of estrogen use [a,b]	Relationship of endometrial cancer to dose of estrogen [a,b]	Relationship of endometrial cancer to recency of estrogen use [a,b]
Hulka (1980a)	Cases were all women who had received their initial therapy for endometrial cancer at North Carolina Memorial Hospital (NCMH) from 1970 through 1976; patients with carcinoma "in situ" were excluded. Cases were 60 years old, on average, at admission. Gynecology controls were women, average age 60 years, with intact uteri selected from the pool of all gynecologic admissions and consultations on surgical or medical services of the NCMH from 1970 through 1976 matched for age, race, and year of admission, and with intact uterus; excluded were women admitted to the gynecologic oncology service and women admitted primarily for curettage or endometrial biopsy. Community controls were a sample of women, average age 55 years, with intact uteri residing in a major referral area of NCMH, and matched for age and racial group. Sources of information included interviews and review of medical records.	256 cases (32.8% estrogen users); 224 gynecology controls (22.9% users); 321 community controls (27.1% users)	White women. 1.8 (0,9-2.5) compared with gynecologic controls; 1.4 (0.9-2.1) compared with community controls Black women: 0.7 (0.3-2.1) compared with gynecologic controls; 1.5 (0.4-5.1) compared with community controls	<3.5 yrs.: 0.8 (0.4-1.7 compared with gynecology controls; 0.7 (0.4-1 .3) compared with community controls >3.5 yrs.: 4.1 (1 ,8-9.6) compared with gynecology controls; 3.6 (1 .9-6.8) compared with community controls	<0,625 mg: 1.6 (NS) compared with gynecology controls; 2.3 (NS) compared with community controls >0,625 mg: 1.8 (NS) compared with gynecology controls, 1.4 (NS) compared with community controls	In comparison of cases to community controls, risk drops to that of non-users of estrogen after a 20-month estrogen-free interval; in comparison to the gynecology control group, excess risk disappeared 28 months after cessation of estrogen.

TABLE G-1: HRT and Endometrial Carcinoma: Hospital-Based Case Control Studies (Page 7 of 17)

Author	Description of cases and controls	Number of cases and controls	Relationship of endometrial cancer to estrogen use [a,b]	Relationship of endometrial cancer to duration of estrogen use [a,b]	Relationship of endometrial cancer to dose of estrogen [a,b]	Relationship of endometrial cancer to recency of estrogen use [a,b]
Hulka (1980b)	Cases were women, mean age 61 years, with endometrial cancer receiving their initial therapy at North Carolina Memorial Hospital (NCMH) between 1970 and 1976. Gynecologic controls were selected from patients admitted to the gynecology service and from patients receiving gynecologic consultations while inpatients on surgical or medical services of the NCMH during 1970 through 1976. Admissions to the gynecologic oncology service, women admitted for dilation and curettage, and women with a previous hysterectomy were excluded. Controls were matched for age, year of admission, and race with cases. Community controls were from a sample of women over 30 years old (mean age 56 years) residing in the major referral areas of NCMH, stratified by age and within racial group. All had intact uteri. Information was gathered from interviews and medical records.	256 cases (32.8% estrogen users), 224 gynecology controls (22.9% users), 321 community controls (27.1 % users)		Duration of estrogen use < 3,5 years: Stage 1A: 1.2 (NS) Stage 1B: 0.9 (NS) Stage 11: 0.7 (NS) Stage III-IV: 0.6 (NS) Grade 1. 1.0 (NS) Grade 2: 0.7 (NS) Grade 3: 0.6 (NS) invasion: myometrium and beyond. 0.5 (NS) Duration of estrogen use >3.5 yrs.: Stage 1A: 7.6 (p< 0,05) Stage IB: 1.6 (NS) Stage Il: 3.3 (p< 0,05) Stage III-IV 1.5 (NS) Grade 1 55 (p< 0,05) Grade 2: 19 (NS) Grade 3 2.9 (p< 0.05)	Estrogen strength=<O.625 mg. Stage 1A: 5.8 (p < 0,05) Stage IB-IV: 2.3 (NS) Grade 1: 4.0 (p< 0.05) Grades 2-3.2.5 (NS) invasion: endometrium: 5.2 (p< 0,05) myometrium and beyond: 2.1 (NS) Estrogen strength > 0.625 mg: Stage 1A: 8.5 (p< 0,05) Stages IB-IV: 1.5 (NS) Grade 1. 5.4 (p< 0,05) Grades 2-3. 2.0 (NS)	Estrogen-free interval > 6 me,, Stage 1A: 2.5 (NS) Stages IB-IV: 1.3 (NS) Grade 1. 2.2 (NS) Grades 2-3: 1.3 (NS) invasion: endometrium. 2.1 (NS) myometrium: 2.0 (NS) Estrogen-free interval < 6 months: Stage 1A. 8.8 (p < 0.05) Stages IB-IV: 2.1 (NS) Grade 1. 6.2 (p < 0,05) Grades 2-3. 2.3 (NS)

TABLE G-1: HRT and Endometrial Carcinoma: Hospital-Based Case Control Studies (Page 8 of 17)

Author	Description of cases and controls	Number of cases and controls	Relationship of endometrial cancer to estrogen use[a,b]	Relationship of endometrial cancer to duration of estrogen use[a,b]	Relationship of endometrial cancer to dose of estrogen[a,b]	Relationship of endometrial cancer to recency of estrogen use[a,b]
				invasion: only endometrium: 5.2 ($p < 0.05$) myometrium and beyond: 2.5 ($p < 0.05$) With long-duration estrogen use, the endometrial cancer risk is high for cancers that are Stage IA, Grade 1, and invading the endometrium only.	invasion: endometrium 5.5 ($p < 0.05$) myometrium and beyond: 2.3 (NS)	invasion: endometrium: 6.5 ($p < 0.05$) myometrium and beyond: 2.4 (NS)
Jelovsek (1980)	Cases were patients, mean age 59 years, with diagnoses of endometrial cancer at Duke University Medical Center (Durham, NC), 1940-1975, identified through the medical records and pathology files, as well as the office records of Duke physicians. One control patient was selected for each study patient from the general registration files of the medical records department (includes both outpatients and inpatients). Control patients were registered within one year at the date of diagnosis of cancer in the study patient, and matched for age, race, and parity; control patients were not hysterectomized. Information was gathered from medical records.	431 cases (12% estrogen users); 431 controls (6% estrogen users)	Odds ratio 2.4 (1.4-3.9) (unmatched)	6 mo.-3 yrs.: odds ratio 1.4 (0.6-3.5) 3 yrs.-5 yrs.: odds ratio 1.4 (0.3-6.5) 5 yrs.-10 yrs.: odds ratio 4.8 (1.6-14.5) > 10 yrs.: odds ratio 2.6 (1.1-5.9)		

TABLE G-1: HRT and Endometrial Carcinoma: Hospital-Based Case Control Studies (Page 9 of 17)

Author	Description of cases and controls	Number of cases and controls	Relationship of endometrial cancer to estrogen use [a,b]	Relationship of endometrial cancer to duration of estrogen use [a,b]	Relationship of endometrial cancer to dose of estrogen [a,b]	Relationship of endometrial cancer to recency of estrogen use [a,b]
Salmi (1980)	Cases were all patients with endometrial cancer diagnosed and treated in the Department of Obstetrics and Gynecology at the University Central Hospital of Turku, Finland, from 1970 to 1976. Controls were women between the ages of 35 and 60 identified from Turku's continuing mass screening program for cervical and breast cancer. Women over 60 were identified from the National Population Registry. There were 585 controls, 282 of which were matched for age, height, weight, and social class. Information on HRT use was gathered by interviews.	318 cases (33% hormone users); 282 matched controls; 585 total controls (43.6% users)	Matched pairs analysis Any use of hormones. 0.6 (0.4-0.9) Use of hormones for gynecological conditions: 0.6 (0.4-0.9) Use of estrogen: 0.4 (0.2-0.7) Estrogen use was defined as use of 6 months or more. Estradiol only or combined with androgen. 0.3 (0.2-0.7) Estriol only. 0.4 (0.1-1 .0) Conjugated estrogens: 5.0 ($p < 0.05$) Other estrogens: 0.6 (0.2-1.4)			

TABLE G-1: HRT and Endometrial Carcinoma: Hospital-Based Case Control Studies (Page 10 of 17)

Author	Description of cases and controls	Number of cases and controls	Relationship of endometrial cancer to estrogen use [a,b]	Relationship of endometrial cancer to duration of estrogen use [a,b]	Relationship of endometrial cancer to dose of estrogen [a,b]	Relationship of endometrial cancer to recency of estrogen use [a,b]
Stavraky (1981)	Cases were all new patients between 40 and 80 years of age with a diagnosis of endometrial carcinoma admitted to Victoria Hospital, London, Ontario between September 1976 and October 1978 for preoperative radiation. Two controls for each patient were selected from the hospital's daily patient register, one control was a woman with a gynecologic disorder, matched for age within.5 years; another control was a woman with a nongynecologic disease within the same age range; hysterectomized women were not included in control group. Information was gathered by questionnaire.	206 cases (58% estrogen users), 191 gynecologic controls (38% users); 199 nongynecologic controls (28% users)	unadjusted relative risk 2.4 (1 ,6-3.7) compared with gynecologic controls unadjusted relative risk 4,3 (2.7-6,7) compared with nongynecologic controls unadjusted relative risk for postmenopausal women only 2,3 (1 ,5-3,7) compared with gynecologic controls unadjusted relative risk for postmenopausal women only 4.8 (2.9-7.7) compared with nongynecologic controls adjusted relative risk[c] 1.5 (0.9-2.7) compared with gynecologic controls	All durations: unadjusted relative risk 2.9 (1 .6-5.1) adjusted relative risk 1.3 (0,5-3.7) Risk by duration of use among patients and gynecologic controls who presented with bleeding: unadjusted relative risk < 2 years: 2.3 (0.5-7,9) 2-4 years: 1,1 (0.5-2.5) 5-9 years: 4.1 (1 .4-10 .5) 1 O+ years, 11,0 (2.1-39.0) adjusted relative risk. O-4 yrs.: 0.7 (O 2-2,5) 5-10+ years: 2.3 (1 .8-8,4) Risk of endometrial cancer among patients and two control groups by duration of estrogen use 14,4 (5,0-41 .8) compared with nongynecologic controls	Gynecologic controls. <0,625 mg 1.9 (0.9-3.6) >0,625 mg 3.1 (1 ,5-6.3) Nongynecologic controls. <0.625 mg 2.9 (1 .4-57) >0.625 mg 6.4 (2.5-14,5)	Use <5 years duration Current users (use within past year). adjusted relative risk 1.3 (0,6-3,1) compared with gynecologic controls; 7,2 (2.6-20.3) compared with nongynecologic controls Past users (cessation of use > 1 year ago): adjusted relative risk 0.5 (0.2-1 .3) compared with gynecologic controls, 1,0 (0,4-2.5) compared with nongynecologlc controls

TABLE G-1: HRT and Endometrial Carcinoma: Hospital-Based Case Control Studies (Page 11 of 17)

Author	Description of cases and controls	Number of cases and controls	Relationship of endometrial cancer to estrogen use [a,b]	Relationship of endometrial cancer to duration of estrogen use [a,b]	Relationship of endometrial cancer to dose of estrogen [a,b]	Relationship of endometrial cancer to recency of estrogen use [a,b]
			adjusted relative risk[c] 4.8 (2.7-8.4) compared with non-gynecologic controls adjusted relative risk[c] for postmenopausal women only 1.5 (0.8-2.8) compared with gynecologic controls adjusted relative risk[c] for postmenopausal women only 4.2 (2,2-8,0) compared with nongynecologic controls Estrogen use was defined as use six months or more.	< 2 years, adjusted relative risk 0.7 (0.3-1.9) compared with gynecologic controls, 1.6 (0,6-4.3) compared with nongynecologic controls 2-4 years. adjusted relative risk 1.0 (0.4-2.2) compared with gynecology controls; 4.0 (1 .6-10 .1) compared with nongynecologic controls 5-9 years: adjusted relative risk 1.7 (0.7-4 1) compared with gynecologic controls; 5.3 (2.2-1 2.4) compared with nongynecologic controls 1 O+ years. adjusted relative risk 6.4 (2.1-19.3) compared with gynecologic controls,		Use >= 5 years duration: Current users. adjusted relative risk 4,3 (1 .9-9,7) compared with gynecologic controls, 11.3 (4.9-25.5) compared with nongynecologic controls Past use. adjusted relative risk 0.7 (0.2-2.7) compared with gynecologic controls, 2.3 (0.6-8.5) compared with nongynecologic controls

TABLE G-1: HRT and Endometrial Carcinoma: Hospital-Based Case Control Studies (Page 12 of 17)

Author	Description of cases and controls	Number of cases and controls	Relationship of endometrial cancer to estrogen use [a,b]	Relationship of endometrial cancer to duration of estrogen use [a,b]	Relationship of endometrial cancer to dose of estrogen [a,b]	Relationship of endometrial cancer to recency of estrogen use [a,b]
Kelsey (1 982)	Cases were women ages 45-74 years old who were admitted from 1977 to 1979 to seven Connecticut hospitals with newly diagnosed endometrial cancer. Controls were other women in the same age group admitted to surgical services (except gynecology) of those hospitals at the same time as the cases. Information on HRT use was obtained by questionnaire.	167 cases (47% estrogen users), 903 controls (38% estrogen users)	Use >5 years: odds ratio 1.6 (1 .3-2,0)	Use <1 yr.: odds ratio 1.1 (no confidence intervals provided) 1-2.5 yrs.: odds ratio 1,0 2.6-5.0 yrs.: odds ratio 2.9 5.1-7.5 yrs.: odds ratio 4.3 7.6-10,0 yrs.: odds ratio 8.2 > 10 yrs,: odds ratio 2.7 (test for trend: p < 0,001)		

TABLE G-1: HRT and Endometrial Carcinoma: Hospital-Based Case Control Studies (Page 13 of 17)

Author	Description of cases and controls	Number of cases and controls	Relationship of endometrial cancer to estrogen us&[b]	Relationship of endometrial cancer to duration of estrogen use [a,b]	Relationship of endometrial cancer to dose of estrogen [a,b]	Relationship of endometrial cancer to recency of estrogen use [a,b]
La Vecchia (1984)	Subjects were women admitted to university and general hospitals in the Greater Milan area between 1979 and 1983. Cases were diagnosed with endometrial cancer within the year prior to interview. Cases were between 33 and 74 years old (median age 60); 30 cases were below 50 years of age. Controls were women less than 75 years admitted for acute conditions unrelated to risk factors for endometrial cancer. Women with gynecological, hormonal, or neoplastic diseases or who had undergone hysterectomy were excluded from controls. Information was gathered by personal interview.	283 cases (25% estrogen users); 566 controls (17% users)	Relative risk 2.3 (1 .6-3.2) adjusted for body mass index and age	There was a significant trend of increasing risk with increasing duration of use (test for trend: p = 0.001). Age <55 years: <2 years use: 1,8 (0.9-3.6) >2 years: 5.1 (1 .5-17.1) (test for trend: p = 0.002) Age 55-64 years: <2 yrs,: 1.5 (0.8-2-6) >2 yrs,: 1,8 (0,7-4.5) (test for trend: p = 0.12) Age >= 65 years: <2 yrs.: 1,6 (0.7-3.5) >2 yrs.: 1,4 (0.4-5.4) (test for trend: p = 0.29)		

TABLE G-1: HRT and Endometrial Carcinoma: Hospital-Based Case Control Studies (Page 14 of 17)

Author	Description of cases and controls	Number of oases and controls	Relationship of endometrial cancer to estrogen use [a,b]	Relationship of endometrial cancer to duration of estrogen use [a,b]	Relationship of endometrial cancer to dose of estrogen [a,b]	Relationship of endometrial cancer to recency of estrogen use [a,b]
Shapiro (1985)	Cases were women with endometrial carcinoma admitted to hospitals in Boston, MA; Philadelphia, PA; Baltimore, MD; Tucson, AZ; New York, NY; Kansas City, MO; San Francisco, CA; and London, Ontario; ages 50-69 years, with no history of other cancers. Controls were other female patients on medical, surgical, and orthopedic wards, ages 50-69 years, with no history of cancer, admitted for conditions judged not to be related to estrogen use. Patients were interviewed between September 1976 and December 1982.	425 cases (31 % estrogen users); 792 controls	Relative risk 3.5 (2,6-4.7) adjusted for age, body-mass index, and geographic area. Estrogen use was defined as use of conjugated estrogen, beginning at least two years prior to the date of interview.	<1 year: 0.9 (0,4-1 ,8) 1-4 years: 2.9 (1 .8-4.7) 5-9 years: 5.6 (3,4-9.3) > 10 years: 10 (5.9-18)		< 1 year since last use. < 1 yr. duration. — 1-4 yrs.: 2.1 (0.9-4.7) 5-9 yrs.: 6.3 (3.0-13) >10 yrs.: 12 (5,9-24) 1-4 years since last use: < 1 yr. duration: 0,6 (0.2-2,0) 1-4 years: 3.1 (1 .3-7,4) 5-9 years: 5.2 (2.1-13) > 10 years: 12 (4.8-32) 5-9 years since last use: < 1 yr. duration: 1,0 (0.3-3.5) 1-4 years: 4.0 (1 .4-12) 5-9 years: 6.3 (2,0-20) > 10 years, 3,7 (0.8-18)

TABLE G-1: HRT and Endometrial Carcinoma: Hospital-Based Case Control Studies (Page 15 of 17)

Author	Description of oases and controls	Number of cases and controls	Relationship of endometrial cancer to estrogen use [a,b]	Relationship of endometrial cancer to duration of estrogen use [a,b]	Relationship of endometrial cancer to dose of estrogen [a,b]	Relationship of endometrial cancer to recency of estrogen use [a,b]
						> 10 years since last use: < 1 yr. duration: 1,2 (0.4-3.6) 1-4 years: 3.5 (1 ,4-8.3) 5-9 years: 4.1 (1 .1-15) > 10 years: —
Buring (1986)	Cases were white women, aged 40-80 years, who were admitted to the Boston Hospital for Women's Parkway Division with first diagnosis of endometrial cancer made between January 1970 and June 1975. Controls consisted of all white women, aged 40-80 years, admitted to the same hospital during the same period for nonmalignant conditions requiring surgery. Information was gathered from hospital and clinic records,	188 cases (39% estrogen users); 428 controls (17%. estrogen users)	Ever use: 2.4 (1 ,7-3,6) current use. 2.8 (1 ,8-4.2) (current use defined as use within the year before index admission)	< 1 yr.: 1,4 (no confidence interval provided) I-4 yrs.: 2.0 5-9 yrs.: 6.4 10+ yrs.: 7.6	0.3 mg, 0.625 mg: 2.7 (1 ,6-4.9) 1.25 mg, 2.5 mg: 3.8 (2.2-6.6)	< 1 yr.: 2,4 (no confidence interval provided) 1 + yrs.: 4.6 1-2 yrs.: 4.2 3-4 yrs.: 5.9 5+ yrs.: 4.5 An excess risk of endometrial cancer was noted to continue among estrogen users who had discontinued 5 or more years ago, although there were small numbers of former users.

TABLE G-1: HRT and Endometrial Carcinoma: Hospital-Based Case Control Studies (Page 16 of 17)

Author	Description of cases and controls	Number of cases and controls	Relationship of endometrial cancer to estrogen use [a,b]	Relationship of endometrial cancer to duration of estrogen use [a,b]	Relationship of endometrial cancer to dose of estrogen [a,b]	Relationship of endometrial cancer to recency of estrogen use [a,b]
Ewertz (1 988)	Cases and controls were women referred for radiotherapy at the Oncology Department II of the Finsen Institute, Copenhagen, Denmark. Cases were ages 44 to 89 years (mean age 66 years) and were identified between October 1977 and December 1978. Controls were patients with cervical cancer, from same hospital, matched for age at diagnosis. Data were derived from hospital records.	149 cases (56% estrogen users); 154 controls (21% estrogen users)	4.7 (2.9-7.7) ever users vs. never users			
Brinton (1993)	Cases were menopausal women, ages 20 to 74 years, newly diagnosed with endometrial cancer between June 1, 1987 and May 15, 1990 from seven hospitals in five areas of the United States. Population controls were matched to the cases for age, race, and residential area, identified by random digit dialing and HCFA data tapes. Information was gathered from home interviews.	300 cases (24% estrogen users); 207 controls (14% estrogen users)	Adjusted relative risk. 3.0 (1.7-5.1) Progestin alone: 1.8 (no confidence interval) Estrogens alone 3.4 (no confidence interval)	Both short- and long-term use elevated the risk of early stage tumors, but an effect on late-stage tumors was seen only for long-term use (relative risk 2.1 (0.7-6.4)).	Associations with dose were inconsistent although women who used low-dose preparations exclusively had the lowest risk. There were no striking relationships according to the type of estrogen or regimen used.	Although the highest risks were for recent estrogen users, persistent excess risks were seen even for those who had discontinued use 5 or more years ago.

TABLE G-1: HRT and Endometrial Carcinoma: Hospital-Based Case Control Studies (Page 17 of 17)

Author	Description of cases and controls	Number of cases and controls	Relationship of endometrial cancer to estrogen use [a,b]	Relationship of endometrial cancer to duration of estrogen use [a,b]	Relationship of endometrial cancer to dose of estrogen [a,b]	Relationship of endometrial cancer to recency of estrogen use [a,b]
Jick (1993)	Cases were female members of Group Health Cooperative of Puget Sound, Washington, ages 50 to 64 with newly diagnosed endometrial cancer between 1979 and 1989. Controls were GHC members matched for age and length of membership in health maintenance organization to cases. Cases were identified from GHC's file of discharge diagnoses tumor registry. Information was gathered from pharmacy records and medical records.	172 cases (44% HRT users); 1,720 COntrols (40% HRT users)	Adjusted rate ratio: Current ERT users: 6.5 (3.1 -13.3) Current PERT users: 1.9 (0.9-3.8) Past ERT users: 1.0 (0.5-2.0) Past PERT users: 0.9 (0.3-3.4)	Estrogen alone: 3-4 years: adjusted rate ratio 1.9 (0.4-8.7) >5 years: adjusted rate ratio 22.0 (6.5-74.1) Estrogen and progesterone: >3 years: adjusted rate ratio 1,3 (0.5-3.4) There was insufficient data for women who had used estrogen and progesterone for more than 5 years.	Estrogen: 0.3 mg: 4.3 (1 .2-15 .6) 0.625 mg: 7.1 (2.8-17.6) 1.25 mg: 8.4 (2.0-36.5) Estrogen and progesterone: 0.3 mg: 1.8 (0.4-8.0) 0.625 mg: 1.6 (0.7-3.6) 1.25 mg: 5.4 (1 .0-30 .7)	
Levi (1993)	Cases were women below 72 years old who were diagnosed with endometrial cancer in the Swiss Canton of Vaud between 1988 and 1992, Controls were women of the same age hospitalized for acute conditions not related to cancer or HRT.	158 cases (38% HRT users); 468 controls (20% HRT users)	Risk-factor adjusted relative risk 2,7 (1 .7-4.1)	Duration of use: >5 years, 5,1 (2.7-9.8)		Recency of use: > 10 years since last use: 2.3 (1 ,2-4.5)

[a] 95 percent confidence intervals are shown in parentheses.
[b] Relationship is relative risk, unless stated otherwise.
c Adjusted for age, residence, number of pregnancies, education level, and menopausal status
KEY: HRT= hormonal replacement therapy; NS = not statistically significant

SOURCE: Off Ice of Technology Assessment, 1995

TABLE G-2: HRT and Endometrial Carcinoma: Population-Based Case Control Studies (Page 1 of 7)

Author	Description of cases and controls	Number of cases and controls	Relationship of endometrial cancer to estrogen use[a,b]	Relationship of endometrial cancer to duration of estrogen use[a,b]	Relationship of endometrial cancer to dose of estrogen[a,b]	Relationship of endometrial cancer to recency of estrogen use [a,b]
Ziel 1975)	Cases were patients diagnosed between July 1, 1970 and December 31, 1974 with endometrial cancer at the Kaiser Permanente Medical Center in Los Angeles and reported to its tumor registry. Controls were identified from membership files of the Southern California Kaiser Foundation Health Plan population who live in vicinity of the Los Angeles facility. Two control subjects were selected for each patient and matched by age, area of residence, duration of Health Plan membership, and intact uterus. Information was gathered from review of medical records.	94 cases (57% estrogen users); 188 controls (15% estrogen users)	Relative risk 7.6 (4.3-13.4)	< 1 year: not enough data 1-4.9 years: 5.6 ($p < 0.01$) 5-6.9 years: 7.2 ($p < 0.01$) > 7 years: 13.9 ($p < 1x10^{-5}$)		
Mack (1976)	All cases of endometrial cancer occurring among residents of Leisure World (California) Retirement Community from 1971 to 1975 were compared to controls chosen from a roster of all women in the same community, matched for age and marital status. Information was gathered from clinic records, telephone interviews, and pharmacy records.	63 cases (89% estrogen users) 396 controls	Any estrogens: 8.0 (3.5-18.1) Conjugated estrogens: 5.6 (2.8-11.1)	1-11 mos.: 2.8 (no confidence interval) 12-59 mos.: 4.5 60-95 mos.: 9.3 96+ mos.: 8.8 dose ≤ 0.625 CEE 1-11 mos.: 6.6 12-54 mos.: 3.4 60-95 mos.: 6.0 96+ mos.: 4.8 dose > 0.625 CEE 1-11 mos.: 0.0 12-59 mos.: 29.8 60-95 mos.: 11.9 96+ mos.: 19.1	Dose ≤ 0.625 mg/day conjugated estrogens: 5.0 (no confidence interval provided) > 0.625 mg/day conjugated estrogens: 9.4	Estrogen-free interval before diagnosis: 0-23 mos.: 7.2 (no confidence interval) 24+ mos.: 3.4

TABLE G-2: HRT and Endometrial Carcinoma: Population-Based Case Control Studies (Page 2 of 7)

Author	Description of oases and controls	Number of cases and controls	Relationship of endometrial cancer to estrogen use [a,b]	Relationship of endometrial cancer to duration of estrogen use [a,b]	Relationship of endometrial cancer to dose of estrogen [a,b]	Relationship of endometrial cancer to recency of estrogen use [a,b]
McDonald (1977)	Subjects were all cases of endometrial cancer among residents in Olmstead County, Minnesota over a 30 year period (1945 to 1974). Cases were 25 years of age and older. Four controls, age-matched and residents of Olmstead County, were selected for each case. Information was gathered from medical records.	145 cases (27% estrogen users); 580 controls (28% estrogen users)	All estrogens: 0.9 (0.6-1.4) Conjugated estrogens: 2.0 (1 .2-3.5)	All estrogens: all durations: 0.9 (0.6-1 .4) >6 mo. 2.3 (1 .4-3.6) Conjugated estrogens: all durations: 2.0 (1 .2-3.5) >6 me.: 4.9 (2.3-1 1.5) > 1 year: 5.3 (2.1-14.4) >2 years: 8.3 (2.9-29.9) >3 years: 7.9 (2.9-21 .2)	Dosage of conjugated equine estrogens: 0.625 mg/day: 1.4 (0.3-5.9) 1.25-2.5 mg/day: 7.2 (3.0-14.9)	
Weiss (1979)	Cases were all female residents of King County, Washington, aged 50 to 74 years with newly diagnosed endometrial cancer between January 1975 and April 1976. Cases were identified from the Cancer Surveillance System, a population-based tumor registry serving western Washington. Controls were white women aged 51 to 74 years from King County Identified from household surveys. Information on HRT use and risk factors was gathered through interviews,	322 cases (81 % ever users); 289 controls (34%. ever users)		Age-adjusted relative risk: 1-2 years 1.2 (0.4-3.7) 3-4 years: 5.4 (2.5-1 1,5) 5-7 years: 4.7 (2.6-8.4) 8-10 years. 11,7 (6.2-21 .8) 11-14 years. 24.2 (1 1,8-49,4) 15-19 years 102 (5.3-20,0) > 20 years, 83 (2.8-24.5)	Age-adjusted relative risk. <0.5 mg per day: 2.5 (1 .1-5,3) 0.6-1.2 mg per day: 8.8 (5.0-12.7) > 1.25 mg per day: 7.6 (5.0-1 1.6)	Time since last use: >8 years: 3.0 (0.9-10.6) 3-7 years: 3.8 (1 .5-9.5) 1-2 years: 5.3 (2.6-10.8) current use: 8.7 (6.4-1 1.8)

TABLE G-2: HRT and Endometrial Carcinoma: Population-Based Case Control Studies (Page 3 of 7)

Author	Description of cases and controls	Number of cases and controls	Relationship of endometrial cancer to estrogen use[a,b]	Relationship of endometrial cancer to duration of estrogen use [a,b]	Relationship of endometrial cancer to dose of estrogen [a,b]	Relationship of endometrial cancer to recency of estrogen use [a,b]
Obrink (1981)	Swedish study comparing use of estrogens among 622 cases of endometrial cancer treated at Radiumhemmet (Stockholm) between 1974 and 1977 with estrogen use of the average female population, represented by a randomly selected sample of 1,866 age-matched controls. Progestin treatment was rare among cases and controls.	622 cases (19.27. estrogen users); 1,866 controls		6-36 months: 7.5% cases, 8.O% controls (NS) 37-72 months: 1 0.3% cases, 2.2% controls (p < 0.001) More than 6 years of treatment was uncommon.		
Spengler (1981)	Cases were newly diagnosed with endometrial cancer between April 1, 1977 and December 31, 1977, and were residents of metropolitan Toronto between 40 and 74 years of age. Cases were identified from the records of the pathology departments of 21 Toronto hospitals. Two age-matched controls were selected from the same neighborhood and type of dwelling as their respective case. Neighborhood controls were obtained by door-to-door canvassing which started at the fourth dwelling to the right of the case's residence and proceeded sequentially around the block or through the apartment building. No control had history of hysterectomy or cancer. Information was gathered by questionnaire and by review of hospital and clinic records.	88 cases (45% estrogen users), 177 controls (22% estrogen users)	Odds ratio 2.9 (1 .7-5,1) Odds ratio matched 3.2 (p= 0.0001) Relative risk (adjusted for age, obesity, age at menopause, nulliparity, and educational level) 3.7 (1 .8-7.6) Estrogen use was defined as use 1 or more months during or after menopause.	1-6 months: 1.4 (0.5-4.4) 7-24 months: 2.6 (1 .0-6,5) 25-60 months: 2.2 (0.7-6.5) >60 months: 8,6 (3.2-23.0)	Conjugated equine estrogens: <1 mg: 2.0 (0,9-4.6) >1 mg: 4.0 (1 .9-8.4) total: 3.0 (1 .7-5.3)	

TABLE G-2: HRT and Endometrial Carcinoma: Population-Based Case Control Studies (Page 4 of 7)

Author	Description of cases and controls	Number of cases and controls	Relationship of endometrial cancer to estrogen use[a,b]	Relationship of endometrial cancer to duration of estrogen use[a,b]	Relationship of endometrial cancer to dose of estrogen[a,b]	Relationship of endometrial cancer to recency of estrogen use [a,b]
Henderson 1983)	Cases were white women from Los Angeles County with endometrial carcinoma diagnosed between January 1972 and December 1979, identified from a regional cancer registry; all cases were aged 45 years or less at diagnosis. Controls were white, age-matched, and selected from same neighborhood as cases. Information on HRT use and risk factors was gathered from telephone interviews.	127 cases (12% estrogen users); 127 controls (7% estrogen users)		< 2 yrs.: 1.38 (NS) > 2 yrs.: 3.13 (NS)		
Pettersson (1986)	Cases were women, mean age 63 years, newly diagnosed in 1980 and 1981 with endometrial carcinoma and living in the Uppsala, Sweden, Health Care region. Controls were age-matched, and from same county of residence as cases. Only a small number had used estrogen-progesterone therapy. Data was collected both by questionnaire and interview.	250 cases (20.1% estrogen users); 253 controls (15.8% estrogen users)	For treatment > 4 years duration. odds ratio 4.5 1.2-17.3)	Odds ratios for durations: < 12 months: 0.9 (0.4-1.8) 13-47 months: 1.1 (0.5-2.4) > 48 months: 4.3 (1.3-13.9)		

TABLE G-2: HRT and Endometrial Carcinoma: Population-Based Case Control Studies (Page 5 of 7)

Author	Description of cases and controls	Number of cases and controls	Relationship of endometrial cancer to estrogen use [a,b]			Relationship of endometrial cancer to recency of estrogen use [a,b]
Lawrence (1989)	Cases were women ages 40 to 69 years from hospitals in upstate New York who had been diagnosed as having advanced-stage (stages 2-4) endometrial cancer in 1979-1981. Controls were selected from the files of licensed drivers maintained by the New York State Department of Motor Vehicles. Two controls were selected for each case, matched by county of residence and age. Information on HRT use was gathered through structured interviews.	84 cases (27% estrogen users); 168 controls (24% estrogen users)	< 1 year: odds ratio 0.84 (no confidence interval) 1-5 years: odds ratio 1.47 > 5 years: odds ratio 2.21	The risk of advanced endometrial cancer increased significantly ($p < 0.05$) with duration of use of estrogen pills. No significant association was found for any other variables or for interaction between longer estrogen use and dosage greater than 0.625 mg, continuous mode of administration, or recency interval (the time interval from the last use of estrogen to diagnosis). Despite a statistically significant correlation between duration of estrogen use and advanced-stage endometrial cancer, estrogen use actually contributed little to the risk of advanced-stage disease. Odds ratio=1.01 (1.00-1.03).	No significant association was found between dose and risk of endometrial cancer.	No significant association was found with recency interval and risk of endometrial cancer.

TABLE G-2: HRT and Endometrial Carcinoma: Population-Based Case Control Studies (Page 6 of 7)

Author	Description of cases and controls	Number of cases and controls	Relationship of endometrial cancer to estrogen use [a,b]	Relationship of endometrial cancer to duration of estrogen use [a,b]	Relationship of endometrial cancer to dose of estrogen [a,b]	Relationship of endometrial cancer to recency of estrogen use [a,b]
Rubin (1990)	Results from Cancer and Steroid Hormone (CASH) Study, a multicenter study conducted in 8 areas of the United States (Atlanta, **GA;** Detroit, MI; San Francisco, CA; Seattle, WA; Connecticut, Iowa, New Mexico, and Utah). Cases were postmenopausal women 40 to 54 years of age who resided in one of the eight areas and who had an endometrial cancer diagnosed between December 1, 1980 and December 31, 1982. Controls were women with an intact uterus, matched for age and geographic area to cases. Information on HRT use was obtained through interview.	196 cases (24% estrogen users); 986 controls (14'%. estrogen users)	1.9 (1 .3-2.8) ever user vs. never user Estrogen use was defined as 3 months consecutive use of estrogen replacement therapy.	<2 yrs.: 1,3 (0.7-2,4) 2-5 years. 2.1 >6 years, 3.5	<0.625 mg per day, 1.2 (0,5-2.7) > 1.25 mg per day, 3.8 (1 .7-8.5)	**Time** since last use < 2 years all use. 1.9 (1 .2-3.2); duration <2 yrs.. 1.4 (07-3.0); duration >= 2 yrs., 2.4 (1 ,3-4.4) Time since last use 2-5 years: all use. 1.5 (0.8-3.1), duration <2 yrs.: 1.1 (0 4-3.3); duration >= 2 yrs.: 2.0 (0.8-4.9) Time since last use >= 6 years. all use. 2.7 (1.1 -6.4); duration <2 yrs.: 1.4 (0.4-5.2); duration >= 2 yrs., 5.4

TABLE G-2: HRT and Endometrial Carcinoma: Population-Based Case Control Studies (Page 7 of 7)

Author	Description of cases and controls	Number of cases and controls	Relationship of endometrial cancer to estrogen use[a,b]	Relationship of endometrial cancer to duration of estrogen use [a,b]	Relationship of endometrial cancer to dose of estrogen [a,b]	Relationship of endometrial cancer to recency of estrogen use [a,b]
Voight (1 991)	Cases were all women diagnosed with endometrial cancer between Jan. 1, 1985 and Dec. 31, 1987 who were residents of King County, Washington, and who were 40 to 64 years of age at diagnosis ; cancer cases were identified through the cancer surveillance system at the Fred Hutchinson Cancer Research Center. Controls were recruited by random telephone digit dialing; controls were nonhysterectomized women who were residents of King County. Information on HRT use was gathered through interviews.	158 cases (38% HRT users); 182 controls (27% HRT users)	Estrogen alone: O.R. 3.1 (1 ,6-5.8) Estrogen plus progesterone: O.R. 1.3 (0.6-2.8) Progestin use <10 days per month plus estrogen: O.R. 2,0 (0.7-5.3) Progestin use >= 10 days per month plus estrogen: O.R. 0.9 (0.3-2.4)	Estrogen only use 23 years: 5.7 (2.5-1 2.8) Estrogen use >3 years plus any use of progestin: 1.6 (0.6-3.9) Estrogen 23 years plus progestin <10 days per me,: 2.4 (0.6-9.3) Estrogen 23 years plus progestin >= 10 days per month: 1.1 (0.4-3.6)		

a 95 percent confidence intervals are shown in parentheses

b Relationship is relative risk, unless stated otherwise.

KEY: NS = not statistically significant,

SOURCE: Office of Technology Assessment, 1995.

TABLE G-3: HRT and Endometrial Carcinoma: Cohort Studies with Internal Controls (Page 1 of 5)

Author	Description of cohorts	Size of cohort	Relationship of endometrial cancer to use and dose of HRT[a,b]	Relationship of endometrial cancer to duration, recency, and latency of HRT use[a,b]
Gambrell (1979)	Participants were postmenopausal outpatients at Obstetrics and Gynecology Clinic, Wilford Hall USAF Medical Center, Texas. Duration of estrogen therapy ranged from 2.5 to 12 years. Recruitment between 1976-1977 was prospective, 1975 recruitment was retrospective.	8,170 patient-years (81% HRT use); 14 endometrial cancer cases	Endometrial cancer incidence (cases per 1,000 pt.-years). Estrogen alone: 6.8/1 ,000 PERT, 0.5/1 ,000 (p <0.01 compared to estrogen) progestin alone: 0/1 ,000 no therapy: 2/1 ,000 (NS compared to estrogen)	
Bush (1983)	Participants were white women, aged 40 to 69 years at baseline, and followed for an average of 5.5 years. All women in the cohort were participants in the Lipid Research Clinics Program Follow-up Study, conducted in 10 North American clinics, between 1972 and 1976. All subjects were examined at initiation, and were followed with clinic visits and review of death certificates. Information on descendants was gathered from medical records and family members.	2,270 white women (593 users, 1,677 nonusers)	Endometrial cancer deaths. Nonusers: 1 death from an unspecified genitourinary cancer. Users: 1 death from uterine cancer,	

TABLE G-3: HRT and Endometrial Carcinoma: Cohort Studies with Internal Controls (Page 2 of 5)

Author	Description of cohorts	Size of cohort	Relationship of endometrial cancer to use and dose of HRT[a,b]	Relationship of endometrial cancer to duration, recency, and latency of HRT use[a,b]
Lafferty (1985)	Cohort members were postmenopausal women 45 to 60 years old followed at a single private practice in Cleveland, OH. All treated patients received conjugated equine estrogen 0.6 mg daily for three out of four weeks. Study was carried out between 1966 and 1981, and patients were followed for an average of 8.6 years. Patients were followed with physical exams twice annually.	61 estrogen-treated women, 63 untreated controls	One case of endometrial cancer occurred in untreated controls, and two in estrogen-treated women. No endometrial cancer deaths occurred in untreated controls and two deaths in estrogen-treated women. The difference in rates of endometrial cancer deaths were not statistically significant, but the population was very small.	
Gambrell (1986)	Participants were post-menopausal women seen at Wilford Hall USAF Medical Center (Texas) using various hormone regimens were compared to untreated women. Three years of retrospective data were gathered for 1972-74 from medical and pharmacy records and tumor registry. Women were recruited between 1975 and 1979, and followed until 1983. Information on HRT use and risk factors gathered at clinic visits.	2,905 postmenopausal women with 27,243 patient-years of observation between 1975 and 1983 (31 endometrial cancer cases).	No use: 245.5 endometrial cancer cases per 100,000 patient-years. Unopposed estrogen: 390.6 per 100,000 (NS vs. no use) Estrogen and progesterone: 49.0 per 100,000 (p <0,0001 vs. unopposed estrogen users) (p =< 0.005 vs. no use) Estrogen vaginal cream: 73.6 per 100,000 users (p <0,005 vs. unopposed estrogen users), None of the differences between the other groups were statistically significant,	

TABLE G-3: HRT and Endometrial Carcinoma: Cohort Studies with Internal Controls (Page 3 of 5)

Author	Description of cohorts	Size of cohort	Relationship of endometrial cancer to use and dose of HRT [a,b]	Relationship of endometrial cancer to duration, recency, and latency of HRT use[a,b]
Stampfer (1986)	Subjects were members of the nationwide Nurses Health Study cohort. Cohort members were registered nurses ages 30 to 55 years old in 1976. Subjects of this study were cohort members who were free of cancer and had intact uteri. Information on HRT use and risk factors was gathered by questionnaire every two years, and deaths were identified through state vital statistics records. There was 114,896 person-years of follow-up among postmenopausal women in cohort.	96,356 women in cohort with intact uterus who were free of cancer at baseline (no information on number of postmenopausal), among postmenopausal women in cohort, there were 70 cases of endometrial cancer in 114,896 years)	Current use of postmenopausal HRT: 4.4 (2,2-7.1); Among past HRT users, there was an increased risk with increasing duration.	Current use and duration of use >5 years: 6.9 (3.6-13.2) Current use and duration of use <1 year. 3.5 (1 .2-10 .8)
Petitti (1987)	Subjects were participants in the Walnut Creek (California) Contraceptive Drug Study. Subjects were 18 to 54 at study initiation, and were recruited between December 1968 and 1972. All subjects received a complete history and physical at study entry. Through 1977, reformation was gathered from clinic visits and mailed questionnaires. From 1978 to 1983, information was gathered from the California Death Index and death certificates. Oral contraceptive users were excluded from this analysis.	3,437 never users of estrogen, 2,656 ever users of estrogen	Endometrial cancer deaths. nonusers: 1 users. 5 RR endometrial cancer death 2.6 (0.4-1 5.5)	

TABLE G-3: HRT and Endometrial Carcinoma: Cohort Studies with Internal Controls (Page 4 of 5)

Author	Description of cohorts	Size of cohort	Relationship of endometrial cancer to use and dose of HRT[a,b]	Relationship of endometrial cancer to duration, recency, and latency of HRT use[a,b]
Pagnini-Hill (1989)	Subjects were non-hysterectomized women, aged 44-100 years (73 median) at baseline from the Leisure World (California) Retirement Community, Subjects were recruited from June 1981 to January 1987. Of estrogen users, 99% had used unopposed estrogen. Average duration of follow-up was 4.6 years. Information was gathered by periodic questionnaires.	5,160 non-hysterectomized women	Risk ratio for endometrial cancer in users is 10 (p < 0,0001) compared with nonusers, No effect of dose on risk was found. The relationship between HRT use and incidence of endometrial cancer is reported in Henderson (1991) (Henderson, 1991),	Recency (years since cessation of estrogen), O-1 years. 25 (9,2-69) 2-7 years: 12 (no confidence interval) 8-14 years: 8.1 (non confidence interval) 15+ years: 5,8 (2.0-1 7) Duration of estrogen use,* < 2 years: 5.2 (no confidence interval) 3-7 years: 7.0 (no confidence interval) 8-14 years: 4 (no confidence interval) 15+ years: 20 (7,2-54)

*Paper also has table showing interaction of duration and years since cessation of therapy

TABLE G-3: HRT and Endometrial Carcinoma: Cohort Studies with Internal Controls (Page 5 of 5)

Author	Description of cohorts	Size of cohort	Relationship of endometrial cancer to use and dose of HRP[a,b]	Relationship of endometrial cancer to duration, recency, and latency of HRT use[a,b]
Henderson (1991)	Participants were residents of a Southern California retirement community (Leisure World), were almost entirely white, moderately affluent, and well educated. Subjects were recruited between June 1981 and January 1987. The resident's median age at study initiation in 1981 was 73 years. Information was gathered by periodic questionnaires and review of local county death certificates. Virtually all HRT users took unopposed estrogen. Reported here are the results of 7.5 years	8,881 postmenopausal women	Relative risk endometrial cancer death: 3.0 (no confidence interval provided) in ever users vs. never users of estrogen. The relationship between use of HRT and endometrial cancer incidence in this cohort is described in Pagnini-Hill (1989) (Pagnini-Hill, 1989),	

[a]95 percent confidence intervals are shown in parentheses
b Relationship is relative risk, unless stated otherwise.

KEY: NS = not statistically significant; O.E. ratio = observed to expected ratio; PERT = estrogen/progestin combination therapy

SOURCE: Office of Technology Assessment, 1995

TABLE G-4: HRT and Endometrial Carcinoma: Cohort Studies with External Controls (Page 1 of 5)

Author	Description of cohorts	Size of cohort	Relationship of endometrial cancer to use and dose of HRP[a,b]	Relationship of endometrial cancer to duration, recency, and latency of HRT use[a,b]
Hammond (1979)	Participants were diagnosed between 1940 and 1969 with diseases related to estrogen deficiency and followed for at least 5 years by the Duke University Obstetrics and Gynecology Service (Durham, NC). Expected rates of endometrial cancer were obtained from the Third National Center Survey for the Atlanta (Southeastern United States) area; 95.5% Of estrogen users received conjugated estrogens. Data on ERT use was obtained from hospital and clinic records.	301 "hypoestrogenic" patients who received ERT; 309 hypoestrogenic patients never receiving estrogen, 14 patients developed endometrial cancer	O.E. ratio 9.3 (4.7-16.7) in white women receiving estrogen: 1.1 (0.3-3.9) in white women not receiving estrogen All patients who developed adenocarcinoma of the endometrium during estrogen therapy had received this compound for at least five years.	
Vakil (1983)	Study examined the incidence of endometrial cancer in a cohort of women, 32-62 years of age, receiving estrogen treatment for menopausal symptoms among the patients of 20 gynecologists in the metropolitan Toronto area. Incidence rates in the cohort were compared to two control groups: the age-specific endometrial cancer incidence rates of the female populations of Ontario and of Saskatchewan. Estrogen therapy was begun between 1960 and 1970, and subjects were followed for up to 17 years	1,483 postmenopausal women	Relative risk of endometrial cancer in ever users 1.3 (no confidence interval provided	

TABLE G-4: HRT and Endometrial Carcinoma: Cohort Studies with External Controls (Page 2 of 5)

Author	Description of cohorts	Size of cohort	Relationship of endometrial cancer to use and dose of HRF[a,b]	Relationship of endometrial cancer to duration, recency, and latency of HRT use [a,b]
Hunt (1987)	This is the same cohort as described in Hunt (1990) (Hunt, 1990). Cohort members were British women receiving hormone replacement therapy recruited at 21 menopause clinics. Subjects were recruited prospectively between 1978 and 1982, and retrospectively before 1978; nearly equal proportions were recruited retrospectively and prospectively. Most cohort members were aged 45-54 years at recruitment. Thirty-six percent of cohort had undergone hysterectomy, 2-2.5 times the proportion in the British population. Mean duration of follow-up was 67 months. Cancer registry rates for England and Wales were used for determining expected incidence.	4,544 British women receiving HRT (43% PERT users)	O.E. ratio of endometrial cancer is 2.84 (1 ,46-4.96) for current users of at least 1 year duration compared with expected incidence. No deaths from endometrial cancer occurred in the cohort. The relationship of HRT use to endometrial cancer death are reported in Hunt (1990), below.	Latency (time since first use): O-4 years. O.E. ratio 2.11 (0.57-5.39) 5-9 years. 3.03 (1.1 1-6.60) 10+ years, 5,71 (0.64-20.63) There was evidence of a rising trend in O.E. ratio with interval since first use, although the trend does not reach statistical significance.

TABLE G-4: HRT and Endometrial Carcinoma: Cohort Studies with External Controls (Page 3 of 5)

Author	Description of cohorts	Size of cohort	Relationship of endometrial cancer to use and dose of HRT[a,b]	Relationship of endometrial cancer to duration, recency, and latency of HRT use[a,b]
Ettinger (1 988)	Subjects were female members of Kaiser Foundation Health Plan, San Francisco, CA, all who had filled at least 2 prescriptions for an oral estrogen preparation and were aged at least 53 years in 1986. Estrogen users were menopausal women whose estrogen therapy was begun within three years of menopause and was used regularly for at least 5 years. Nonuser controls were women who had undergone spontaneous (nonsurgical) menopause, were identified from pharmacy records of health plan and were matched for age and length of membership in health plan. Mean age for estrogen users was 67 years, mean age of nonusers was 68.8 years. Clinical material was obtained from 1965 to 1980.	181 estrogen users, 220 nonusers controls	Risk ratio for endometrial cancer is 7.7 (2.4-24.5) for users compared with nonusers. Endocarconima developed in 9.9% of users compared with 1.4% of nonusers.	

TABLE G-4: HRT and Endometrial Carcinoma: Cohort Studies with External Controls (Page 4 of 5)

Author	Description of cohorts	Size of cohort	Relationship of endometrial cancer to use and dose of HRT [a,b]	Relationship of endometrial cancer to duration, recency, and latency of HRT use [a,b]
Persson (1989)	Cohort members were women age 35 years or older who had been prescribed estrogens for the treatment of menopausal problems in the Uppsala health care region of Sweden during April 1977 to March 1980, identified through prescription records. Compliance, sociodemographic data, and lifetime exposures to estrogen and progesterone were assessed by a mailed questionnaire to 735 randomly selected members of the cohort. In addition, characteristics of all women with endometrial cancer were assessed by questionnaires. Cases of endometrial cancer were identified from a cancer registry and medical records. Expected outcome in the cohort was determined from age-specific incidence rates of endometrial cancer in the region in the same years. Pathologic specimens from all endometrial cancers and pre-malignant lesions in the cohort and the background population were reviewed. Average observation period	23,233 women on estrogens (133,373 person-years); 74 cases of endometrial cancer and 33 pre-malignant lesions	All HRT users: 1.4 (0.4-2.1) estrogen alone. 1.4 (1.1 -1 .9) estrogen and progestin: 0.9 (0.4-2.0)	Duration of estrogen use: estrogen alone. <6 mos.: 1.1 (0.5-2,5) 7-36 mos.: 1.4 (0,8-2.4) 37-72 mos.: 1.2 (0.6-2.2) >73 mos., 1,8 (1,1 -3.2) estrogen and progestin: <6 mos.: O (0,0-1 2.7) 7-36 mos.: 1.4 (0.5-3.6) 37-72 mos.: 1.2 (0.3-5.5) >73 mos.: O (0,0-456.1) Endometrial cancer and pre-malignant lesions estrogen alone. <6 mos.: 0,9 (0,4-2,1) 7-36 mos.: 1.6 (1 .0-2.5) 37-72 mos.: 1.6 (1 .0-2.6) >73 mos.: 2,7 (1 ,8-4,2) estrogen and progestin: <6 mos.: 0,9 (0.2-4.3) 7-36 mos.: 1.6 (0.7-3.5) 37-72 mos.: 0.9 (0.2-4.1) >73 mos.: O (0.0-211 8)

TABLE G-4: HRT and Endometrial Carcinoma: Cohort Studies with External Controls (Page 5 of 5)

Author	Description of cohorts	Size of cohort	Relationship of endometrial cancer to use and dose of HRT[a,b]	Relationship of endometrial cancer to duration, recency, and latency of HRT use[a,b]
Hunt (1990)	This is the same cohort as described in Hunt (1987) (Hunt, 1987). Subjects were women recruited from 21 menopause clinics around Britain; all had received at least 1 year continuous treatment with hormonal replacement therapy before recruitment, All subjects were interviewed at recruitment. Most subjects were age 45 to 54 at first use of HRT. Mean duration of HRT use was 66.9 months; 59& were current estrogen users. The observed mortality was compared to the expected rates in the female population of England and Wales.	4,544 long term users of HRT (43% PERT users)	Observed endometrial cancer deaths. O expected endometrial cancer deaths: 2,70 (taking into account uterine status) O/E ratio: 0.00 (0.00-0.97) The previous report, Hunt (1987), however, noted an elevated risk of incident endometrial cancer (see above)	

[a] 95 percent confidence intervals are shown in parentheses.
b Relationship is relative risk, unless stated otherwise

KEY: NS = not statistically significant; O.E. ratio = observed to expected ratio; PERT = estrogen/progestin combination therapy,

SOURCE" Office of Technology Assessment, 1995

Appendix H: Evidence on HRT and Gallbladder Disease

H

There are several theoretical reasons to expect a causal link between estrogens and gallbladder disease. In particular, estrogens increase the risk of gallstone formation. Gallstones form in the gallbladder, a muscular sac in the abdomen that stores and releases bile, a substance that aids in fat digestion. Gallstones are solidified bile. Bile is highly saturated with cholesterol, and it is thought that estrogen raises the concentration of cholesterol in bile, increasing the risk of stone formation (2). Thus, one would expect an increased prevalence of gallstones and symptomatic gallbladder disease in estrogen users (1 1).[1]

Tables H-1 to H-4 summarize the clinical studies evaluating the relationship between gallbladder disease and HRT. A small number of studies have shown that the incidence of symptomatic gallbladder disease increases approximately twofold in current users of oral estrogen replacement therapy. The first report of an association came from a case-control study conducted in the mid- 1970s by the Boston Collaborative Drug Surveillance Program, which showed an increased incidence of surgically confirmed gallbladder disease in current users of either oral contraceptive or oral estrogen replacement therapy (3).[2]

One of the two prospective cohort studies of estrogen replacement therapy and gallbladder disease found that women who were current or past users of noncontraceptive estrogen had an age-adjusted relative risk of symptomatic gallstone dis-

[1] It is not known whether estrogens not taken by mouth would also increase the risk of gallstones. Some argue that estrogen taken by skin patch or injection would not increase the risk of gallstone formation because estrogen taken by nonoral routes does not pass directly from the intestine to the liver. By avoiding the first-pass effect on liver metabolism, nonoral routes of estrogen administration may reduce this increased risk. A study by D'Amato and colleagues compared the effect of 17-beta estradiol given by skin patch and estradiol valerate given by mouth on bile lipid levels in a postmenopausal woman (4). While both therapies increased the cholesterol level in the bile, only oral estrogen induced the formation of cholesterol crystals.

[2] The Boston Collaborative Drug Surveillance Program study was criticized for using hospitalized controls, one half of whom were being treated for fracture or some other orthopedic problem. One commentator has argued that, since women with osteoporosis are less likely to be taking estrogen replacement therapy, this design could have led to a spuriously low rate of estrogen use in the comparison group, compared with usual use in the cases, and thereby a falsely elevated relative risk (1).

TABLE H-1: Hormone Replacement Therapy and Gallbladder Disease: Case-Control Studies (page 1 of 2)

Author	Description of cases and controls	Number of cases and controls	Results[a]
Boston Collaborative Drug Surveillance Program (1974)	Cases were postmenopausal women 45 to 69 years old with a diagnosis of "cholelithiasis" or "cholecystitis" and subsequent cholecystectomy, who were admitted to general medical and surgical wards of 24 hospitals in the Greater Boston area between January and November 1972. Patients with diseases that might either contraindicate estrogen therapy or be related to their use were excluded. Controls were hospital patients without a diagnosis of gallbladder disease, venous thromboembolism, or breast tumors,	152 cases, 774 controls	Relative risk 2,5 (1 .5-4,2), there was "no evidence of a relation with duration of use in postmenopausal estrogen users. "
Honore (1980)	Cases were 262 perimenopausal women (ages 41 to 60 years) with symptomatic gallbladder disease treated by cholecystectomy from 1975 to 1978 at a hospital in Newfoundland, Canada, and diagnosed pathologically as having cholesterol gallstones. A control group, matched for age, consisted of women treated surgically for diseases that have no known association with estrogen replacement therapy. Information on HRT use was obtained from a review of medical records.	262 cases; 290 controls	Relative risk 3.72 ($p < 0.005$). There was a significantly greater incidence of gallbladder disease in obese HRT users than in nonobese HRT users ($p < 0.05$),
Scragg (1984)	Cases were patients in 2 public hospitals in Adelaide, Australia with gallstone disease diagnosed by ultrasound or cholecystectomy between December 1978 and September 1980, Two control groups were used for comparison. Hospital controls were women who were hospitalized and had negative cholecystograms. Community controls were women from the community, matched to cases for age and area of residence.	200 cases, 234 hospital controls, 82 community controls	Mean duration of estrogen use was not substantially different between cases and both control groups
Kakar (1988)	Subjects were women ages 41 to 74 enrolled in a prepaid health plan in western Washington's Group Health Cooperative of Puget Sound Cases were women who underwent gallstone surgery between January 1979 and September 1988. Controls were matched for sex, age, and residence with cases.	102 cases, 98 controls	Relative risk 1 18 (0,65-2,13) for users of 1 year or more vs nonusers, Standardization for the effects of age, race, obesity, parity, thiazide use, and diagnosis of high blood pressure did not alter appreciably the estimate of relative risk.

TABLE H-1: Hormone Replacement Therapy and Gallbladder Disease: Case-Control Studies (page 2 of 2)

Author	Description of cases and controls	Number of cases and controls	Results[a]
LaVecchia(1992)	Subjects were women admitted to one of four hospitals in Milan, Italy between 1987 and 1990. Cases were women, ages 23 to 74 (median age 54), who underwent cholecystectomy, and were discharged with the diagnosis of cholelithiasis or cholecystitis. Controls were women, ages 21 to 74 (median age 54), admitted for acute diseases other than digestive or hormonal diseases or those potentially influencing the use of female hormone preparations.	235 cases; 583 controls	Users of any duration: unadjusted relative risk: 1.7 (0.9-3,1) adjusted relative risk[b]: 1.9 (1 ,0-3.6) Use less than 2 years: unadjusted relative risk: 1.7 (0.8-3.6) adjusted relative risk[b]: 1.8 (0.9-4,2) Use 2 or more years: unadjusted relative risk: 1.3 (0.5-3.8) adjusted relative risk[b]: 1.5 (0,5-4.5) Less than 10 years since last use: unadjusted relative risk: 1.1 (0.5-2.7) adjusted relative risk[b]: 1.3 (0.5-3,3) Last use 10 or more years ago: unadjusted relative risk: 2.3 (1 ,0-5.3) adjusted relative risk[b]: 2.4 (1 ,0-5.1)

[a]The results are followed by 95% confidence intervals in parenthesis.
b Relative risk was adjusted for age, education, area of residence, body mass index, parity, and age at menopause.

SOURCE: Office of Technology Assessment, 1995.

TABLE H-2: Hormone Replacement Therapy and Gallbladder Disease: Cross-Sectional Studies

Author	Description of study participants	Number of participants	Results[a]
Diehl (1980)	Subjects were obtained from a review of a sample of medical records from patients enrolled in the Family Health Center of the University of Texas Health Sciences Center at San Antonio. Gallbladder disease was defined as history of cholecystectomy, gallbladder surgery, or abnormal cholecystogram.	1,018 records	"No trends in the prevalence of gallbladder disease were seen in relationship to use of conjugated estrogens. Our failure to find associations with estrogen-containing drugs may be related to our inability to quantitate their cumulative use in our study population. "
Petitti (1981)	Subjects were adult female twins who volunteered to undergo a health examination for a study. Subjects were considered to have gallbladder disease if they answered "yes" to the question, "Has a doctor ever told you that you have had gallstones or gallbladder trouble?"	868 female twins	Relative risk 2.0 (1 .1-3.6) for history of physician-diagnosed gallbladder disease in estrogen users versus nonusers.
Pixley (1 985)	Subjects were women aged 40 to 69 registered at two Oxford, England general practices. All subjects were screened with ultrasound for gallstones. Gallbladder disease was defined as cholelithiasis on ultrasound cholecystectomy.	632 women recruited from general practice registers and 130 vegetarians.	Study concludes "no association [of gallstones] was found with parity or use of exogenous estrogens. " No further information or statistical analyses was provided on this issue.
Jorgensen (1988)	Subjects were a random sample of women from Copenhagen county, Denmark, ages 30, 40, 50, and 60 years, drawn in 1982 from the National Person Register. Subjects were examined and/or interviewed by telephone or mailed questionnaire. Examined patients received ultrasonography to identify current gallstone disease.	2,301 women	Odds ratio 1.02 (0.25-4.26) for current or past gallbladder disease in estrogen users versus nonusers. Odds ratio 1.86 (0.89-3.86) for estrogen users of 8 or fewer years versus users of more than 8 years.

a The results are followed by 95% confidence Intervals in Parentheses unless otherwise specified

SOURCE: Office of Technology Assessment, 1995

TABLE H-3: Hormone Replacement Therapy and Gallbladder Disease: Prospective Cohort Studies

Author	Description of study participants	Size of cohort	Results[a]
Petitti (1 988)	Subjects were women 18 to 54 years old at time of entry into the Walnut Creek (California) Contraceptive Drug Study cohort between December 1968 and February 1972. Women who ever used oral contraceptives were excluded from this analysis. Women with a previous cholecystectomy were also excluded from this analysis. Results of 10 to 13 year followup are presented. Patients were examined at initiation of study and followed by examination, questionnaire and/or reexamination. Cases were women who underwent cholecystectomy for cholelithiasis or cholecystitis.	16,638 women	All ever users: unadjusted relative risk 2.4 (1 .7-3.2) age-adjusted relative risk 2.1 (1 .5-3.0) past users[b]: unadjusted relative risk 1.8 (1.1 -2.9) age-adjusted relative risk 1.6 (1.1 -2.5) current users: unadjusted relative risk 3.1 (2.2-4.9) age-adjusted relative risk 2.7 (1 .8-4.0) There was no evidence of a relationship of incidence of cholecystectomy with duration of estrogen use.
Grodstein (1 993)	Subjects were postmenopausal U.S. registered nurses who were enrolled in the Nurses Health Study. Information on postmenopausal estrogen use and cholecystectomy was gathered by mailed questionnaires every two years. Duration of follow-up was 8 years.	54,845 postmenopausal women	Current users: risk-factor adjusted relative risk 2.1 (1.9-2.4) Current users of 10 years or more. risk-factor adjusted relative risk 2.6 (2.2-3.1) Current users of 1.25 mg CEE per day or more: risk-factor adjusted relative risk 2.4 (2.0-2.9) Past users of less than 2 years duration. relative risk 1.4 adjusted for recency of use Past users of 10 or more years: relative risk 1,7 adjusted for recency of use Most recent use 1 to 2.9 years ago. risk-factor adjusted relative risk 1.6 (1.2 to 2.0) Most recent use 5 or more years ago. risk-factor adjusted relative risk 1.3 (1.1 to 1.6)

[a] The results are followed by 950/0 confidence Intervals in parenthesis
b Author notes that "We reviewed the medical records at the 39 past estrogen users who had cholecystectomies after 1977 and discovered that 12 Of them had reinitiated estrogen use after 1977 and before their hospitalization for gallbladder disease When those 12 women were removed from the cases that had been considered past users, the age-adjusted relative risk of gallbladder disease in past users decreased to 1.1 (95% confidence interval 0.7-1.8) When these 12 women were added to the current users, this relative risk estimate for current use increased to3 9 (95% confidence interval 2,6-5 .9. As study subjects who never experienced cholecystectomy and who initiated estrogen use after followup could not be relocated, these risk estimates where biased downward for past estrogen use and upward for current estrogen use "
KEY: CEE = conjugated equine estrogen

SOURCE Office of Technology Assessment, 1995

TABLE H-4: Hormone Replacement Therapy and Gallbladder Disease: Randomized Trial

Author	Description of study participants	Duration of study	Results
Nachtigall (1979)	Subjects were 84 pairs of postmenopausal inpatients at Goldwater Memorial Hospital in New York City, a hospital for chronic diseases, matched for age and diagnosis. Treatment group received 2.5 mg CEE daily with 10 mg medroxyprogesterone acetate for 7 days each month. Control group received placebos.	10 years	Incidence of cholelithiasis[a] in treatment group: 4/84 (0.48%) Incidence of cholelithiasis control group 2/84 (0.24%) P>=0.05 (nonsignificant[b])

[a] Author did not define "cholelithiasis."
[b] Author notes "These findings, however, should be interpreted with Caution Since the power of the test differences was generally low due to the small sample size."

SOURCE: Off Ice of Technology Assessment, 1995

ease of approximately 2.1, while current users had a relative risk of 2.7 (16) (table H-3). The other cohort study found, after adjusting for confounding factors, a relative risk of cholecystectomy of 2.6 in long-term current estrogen users. The only controlled clinical trial of estrogen use and gallbladder disease found doubled the incidence of gallbladder disease in HRT users (12) (table H-4). This difference did not reach statistical significance, which may be due to the small number of women who participated in this study.

Some studies of symptomatic gallstone disease, however, have found no effect of estrogen use on gallbladder disease (9). The differences among studies may be due to differences in the doses of estrogens used by participants, the average duration of use of estrogen, or the small numbers of persons involved in these studies (14). These studies also were either case-control studies or cross-sectional studies, which may have biased their outcomes.

Although the strongest evidence, including the prospective cohort studies of the issue, points to an elevated risk of symptomatic gallstone disease among current users, it is less certain whether the risk of symptomatic gallstone disease remains elevated in those who have ceased estrogen therapy. The studies to date have not found a statistically significant relationship between past use and gallstone disease.

Although empirical studies have found an increase in symptomatic episodes, hospitalization, and gallbladder removal (cholecystectomy) among current estrogen users, they have failed to detect an increased prevalence of gallstones among estrogen users using imaging techniques capable of detecting silent gallstones (6,11,17). The failure to find increased incidence of asymptomatic gallstones raises the possibility that the studies examining symptomatic disease may be subject to surveillance biases (i.e., estrogen-treated women are seen more frequently by their doctors and are therefore more likely to be diagnosed and undergo surgery) (l).

Studies have not been able to consistently demonstrate an increased risk of gallbladder disease with increased duration of use of estrogen replacement therapy (3, 16, 16a). Results from the Nurses Health Study cohort demonstrated an increased risk with duration of use in current users, but little or no effect of duration in past users (16a) (table H-3).

The results from the Nurses Health Study also showed an increased risk with larger doses of estrogen (16a). This result is consistent with an earlier cohort study of oral contraceptive users that found an increase in risk with increasing dose (19).

The addition of progestins is unlikely to mitigate estrogen-induced increases in gallbladder

disease, since progestins also promote gallstone formation (11).

On the basis of the studies outlined in tables H-l to H-4, including the cohort studies of this issue(16), 0TA adopted a base case assumption that the risk of symptomatic gallbladder disease would be elevated by a factor of 2.5 while a woman is on HRT. The risk would subside to that of the general population of women at the time that HRT ceases. We believe that the possible values of the relative risk of symptomatic gallbladder disease due to current HRT range from 1.0 (best case) to 3.0 (worst case).

The definitive treatment for gallbladder disease is cholecystectomy, a standard surgical procedure that is rarely fatal (13). For this analysis, we have assumed that gallbladder disease results in health care costs for surgical removal of the gallbladder and hospitalization. We have assumed, however, that gallbladder disease does not affect the years of life lived.

OTA's sensitivity analysis shows that our assumptions about the risk of gallbladder disease in HRT users does not affect the outcome of the analysis greatly, since gallbladder disease affects health care costs but not years of life lived.

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Appendix I: Evidence on HRT and Coronary Heart Disease

I

Coronary heart disease (CHD) is the leading cause of death among U.S. women, surpassing the rates from cancer and other diseases (13). Any change in the risk of CHD due to hormone replacement therapy (HRT) would profoundly alter the risk-benefit equation of HRT.

Prior to menopause, women have a lower incidence of CHD than men. The Framingham study showed that men had three times the incidence of heart disease of age-matched premenopausal women (50). Women within the first few years after natural menopause have no substantial increased risk of heart disease over premenopausal women (21). However, by age 70, the incidence of CHD is approximately the same in women and men. Moreover, after surgical or premature menopause women develop a substantially increased risk of CHD at an earlier age than women who undergo natural menopause at a later age (89).

HOW ESTROGEN MAY AFFECT CHD

One mechanism for a possible beneficial effect of estrogen against CHD is the ability of estrogen to favorably alter lipoprotein levels. Estrogen use has been shown to increase the level of high density lipoprotein cholesterol (HDL) (8,16,23,53,57, 75,101). Studies have demonstrated that serum concentrations of HDL are inversely related to the development of CHD (57,75). Estrogens also lower the serum concentration of low density lipoprotein cholesterol (LDL), and LDL levels are directly related to the development of coronary heart disease (8,15,16,23,46,53,57,86,).

The Lipid Research Clinics Follow-up study showed that women using conjugated equine estrogens at the usual doses indicated for postmenopausal women had HDL levels 16.8 percent higher than women not taking estrogens (15). Estrogen users also had LDL levels approximately 7 percent lower than those of nonusers. Coronary heart disease deaths were reduced by 65 percent in estrogen users compared with nonusers. The investigators concluded that this benefit was substantially mediated by the increase in HDL levels.

Recent research has demonstrated that elevations of HDL and decreases in LDL may also occur with percutaneous and subdermal estrogen administration (46,105). However, there is evidence that transdermal estrogens do not produce the same degree of favorable alterations of lipoprotein cholesterol levels as oral estrogens (10, 20,1 15). Oral estrogen has a much greater lipid effect (increasing HDL, decreasing LDL) than a comparable transdermal dosage, perhaps because of higher concentrations of estrogen in the portal circulation of the liver with oral therapy.

The cardioprotective effect of hormone replacement therapy may also be mediated through lowering lipoprotein(a), an independent risk factor for heart disease in postmenopausal women (69,95,100).

There is evidence that estrogen protects the heart by reversing other changes in metabolism that occur at menopause (106). Estrogen has been found to reverse the unfavorable effects of menopause on glucose and insulin metabolism (69,74). Central obesity is linked to heart disease risk, and estrogen may reverse the changes in body fat distribution that results from loss of estrogen production at menopause (106).

Estrogen may also exert its heart protective effects by favorably altering the balance between coagulation and fibrinolysis (18,82,97), by inhibiting platelet function (5), or by relaxing arterial walls (58,124).[1] Estrogen increases production of prostacyclin, a prostoglandin in the arterial wall (82) that reduces platelet aggregation (70) and causes dilatation of the blood vessels (124). In coronary artery occlusion, the release of thromboxane may induce the aggregation of platelets and reduce blood flow. Prostacyclin counteracts the effect of thromboxane by reducing platelet aggregation and increasing blood flow, and in this way may reduce the risk of coronary artery occlusion.

Estrogen may also protect the heart by favorably altering cardiovascular hemodynamics. Receptors for estrogen have been found on arterial walls (52,68), and estrogen may directly relax the arteries throughout the body (22,25,58). By reducing the resistance to blood flow through the arteries, the work load on the heart is reduced (22). By reducing the workload of the heart, its oxygen needs are reduced. Thus, there is less likelihood that the oxygen requirements of the heart will exceed the oxygen that is available from blood flowing through partially occluded coronary arteries (87).

Rosano demonstrated in a clinical trial the immediate effect that estrogens have on heart disease (87). The investigators studied the acute effect of sublingual estradiol on exercise tolerance and angina in 11 women with coronary artery disease. The women did two exercise treadmill tests (EKG) on two separate days. Forty minutes before each test, they took sublingual estradiol or placebo, in random order. Six patients developed exertional angina and EKG changes after administration of sublingual estradiol, whereas all 11 developed angina and EKG changes on placebo. The authors posited that this immediate beneficial effect of estrogens maybe due to a direct coronary artery relaxant effect of estrogen, dilation of peripheral arteries and arterioles, or to a combination of these mechanisms.

EVIDENCE ON ERT AND CHD

All but four of the more than 30 studies that have evaluated the effect of estrogen replacement therapy (ERT) on coronary heart disease (CHD) **have** shown a reduced risk in estrogen users. The following is a discussion of the evidence on the relationship between ERT and cardiovascular disease risk. Coronary evidence falls into five categories based on methods and data sources:

- hospital-based case-control studies,
- population-based case-control studies,
- prospective cohort studies,
- cross-sectional studies, and
- randomized clinical trials.

Each is discussed in turn.

Hospital-Based Case-Control Studies

The earliest studies examining the risk of coronary heart disease in noncontraceptive estrogen users used as "cases" individuals hospitalized for myocardial infarction (heart attack) over a specified time period. "Controls" were a comparison group of patients with other diagnoses from the

[1] For recent reviews of the potentially important nonlipoprotein-mediated mechanisms of reduction in coronary heart disease risk, see K.F. Ganger, B.A. Reid, D. Crook, et al., 1993; M. Riedel, W. Raffenbeul, and P. Lichtlen, 1993; J.C. Stevenson, D. Crook, I.F. Godsland, et al., 1994; M.J. Tikkanen, 1993.

same hospitals as the cases. The researchers then determined which women in each group had or had not had ERT in the past through interviews with the women, medical records, and other sources.

Five hospital-based case-control studies have examined ERT among patients hospitalized for myocardial infarction. (See table I-1.) Of these, one showed an increased risk of coronary heart disease among estrogen users (48), two showed virtually no change in risk (88,91), and two showed a decreased risk of CHD that was not statistically significant.[2]

A well recognized problem with case-control studies is that the ascertainment of exposure to the agent in question (e.g., estrogen) often depends on the recall of the study participants. Because cases may differ from controls in the accuracy of recall of exposure, a biased estimate of risk can occur.

A second problem particular to hospital-based case-control studies is that a control group composed of hospitalized patients is not likely to be representative of the general population from which the cases were drawn with regard to exposure to estrogen. In the context of ERT, the results of hospital-based case-control studies are difficult to interpret because many diseases are related in some way to estrogen use. For example, some members of the control group may have been hospitalized because of fracture, and women with fracture are less likely to have used estrogen.

Even selecting controls from patients with diseases unrelated to estrogen use is problematical, because some physicians may be less willing to prescribe ERT to patients who are already burdened with other medications (103). The net effect of this last bias would be to underestimate the impact of estrogen on heart disease risks.

The first case-control study that did not detect a lower risk of CHD in estrogen users was of hospitalized patients aged 40 to 75 enrolled in the Boston Collaborative Drug Surveillance Program. The relative risk of nonfatal myocardial infarction (MI) in estrogen users was 0.47, but the relative risk was not significantly different from one after statistical adjustment for differences in heart disease risk factors between the two groups (88). Also, heart disease risk is thought to be more markedly reduced among those who are currently using estrogen ("current users") compared with those that have used estrogens in the past (14), and only eight of the 336 cases in the study (2 percent) were "current users" of estrogens.

The second study finding no decreased risk was of women aged 30 to 49 years old admitted to hospital coronary care units (91). The adjusted relative risk was near one both in patients who had ever used estrogen ("ever users") and in "current users." The results of this study may not be generalizable to all postmenopausal women because it was conducted among women under 50 years of age. Because of their young age, these women had infrequent use of ERT and were at minimal risk of coronary heart disease. Moreover, a substantial proportion of controls in this study were fracture patients (13,103).

Jick and colleagues reported the highest relative risk of coronary heart disease in estrogen users among all studies (48). They reported a relative risk of first nonfatal MI of 7.5 (95 percent confidence intervals 2.4 to 24) among estrogen users under 46 years of age and a relative risk of 4.2 (95 percent confidence intervals 1.0-18.8) among postmenopausal estrogen users. This study had a small number of cases and a large loss of study participants over time. Sixteen of the 17 cases (94

2 The change in risk of disease in these studies is expressed either as a relative risk or as an odds ratio (42,94). The odds ratio is obtained from the exposure ratio in the cases divided by the exposure ratio in the controls. To determine the odds ratio in a hospital-based case-control study of myocardial infarction and estrogen use, one would calculate the ratio of estrogen users to nonusers among myocardial infarction patients (cases) and divide that by the ratio of estrogen users to nonusers in the comparison patients hospitalized with other diagnoses (controls). Results of a case-control study can also be expressed as a relative risk, which is the rate with which the disease occurs in exposed people divided by the rate of the disease's occurrence in unexposed people. If these two rates of occurrence are very small and if no distortions have occurred in the four groups that make up the case-control study, the odds ratio will be approximately equal to the risk ratio.

TABLE I-1: Postmenopausal Estrogen Use and Coronary Heart Disease Hospital-Based Case-Control Studies (page 1 of 3)

Author	Description of study	Number of study subjects	Measured endpoint	Relationship of hormonal replacement therapy to heart disease endpoints[a,b]
Rosenberg (1976)	Cases were two sets of patients hospitalized for myocardial infarction in the Boston Collaborative Drug Study. First set of cases was from 21 hospitals in the United States, Great Britain, Canada, Germany, New Zealand, Italy, and Israel, admitted since 1969, Second set was from general medical and surgical wards of 24 Boston hospitals in 1972. Study subjects were ages 40 to 75 years; average age 54 years. Controls were patients from same hospital admitted for neoplasm, gallbladder disease, and breast or reproductive organ disease. Data were obtained from interviews and hospital records. Current use was defined as use during the month prior to hospitalization.	Cases (set 1: 163; set 2: 173) (2.4% conjugated estrogen users); controls (set 1: 2,536; set 2: 4,194)	Nonfatal MI	Current users: age-adjusted relative risk 0.71 (0.34-1 .46) risk-factor adjusted* relative risk 0.97 (0.49-1 .95) *adjusted for age, history of MI, angina, diabetes, hypertension, and smoking
Jick (1 978a)	Cases were women ages 39 to 45 years of age discharged within the first 6 months of 1975 with a diagnosis of AMI. Cases were identified from a national hospital discharge database. Controls were drawn from the national hospital discharge database, were about the same age as cases, were hospitalized for acute illnesses (other than MI) or elective surgery, and were discharged about the same time as cases. Both cases and controls had no other illnesses that predisposed to MI or contraindications to estrogen use. Cases and controls had a natural menopause, hysterectomies, or tubal ligation, or their husband had a vasectomy. Current estrogen use was defined as use of noncontraceptive estrogens within 3 months of admission.	17 cases (53% estrogen users); 34 controls (12% estrogen users)	First nonfatal MI	Current estrogen use: 7.5 (90% confidence interval 2.4 to 24) adjusted for type of sterilization Ninety-four percent of cases, but only 47% of the controls, were cigarette smokers.

TABLE I-1: Postmenopausal Estrogen Use and Coronary Heart Disease Hospital-Based Case-Control Studies (page 2 of 3)

Author	Description of study	Number of study subjects	Measured endpoint	Relationship of hormonal replacement therapy to heart disease endpoints[a,b]
Jick (1 978)	Cases were women ages 35 to 45 discharged during the first 6 months of 1975 with a diagnosis of AMI. Cases and controls were identified from a national hospital discharge database. Controls were women about the same age as cases, who were hospitalized for acute illnesses (other than MI) or surgery, and discharged about the same time as cases. Results are reported for cases and controls who had no serious chronic illnesses (other than MI in cases) or contraindications to estrogen use. Current use was defined as use of noncontraceptive estrogens within three months of admission.	19 cases (53% estrogen users), 39 controls (10% estrogen users)	First nonfatal MI	Current estrogen use 9.3 (lower 95% confidence interval 3.1) adjusted for menopausal status
Rosenberg (1980)	Cases were women ages 30 to 49 years of age selected from interviews between July 1976 and April 1979 with a discharge diagnosis of first MI. Hospitals were located in Greater Boston, Long Island, New York, and the coastal area of northern New York City and the Delaware Valley. Controls were selected from the same hospitals as cases but did not have a discharge diagnosis of MI. Information was gathered by nurse interviewers. Current use was defined as use within the month preceding admission,	99 cases post menopausal (18% current users) (24% past users); 463 controls	First MI	Current users: age-adjusted relative risk 1.39 (0.71 -2,74)
Szklo (1 984)	Cases were white female patients 35 to 64 years of age admitted to 5 general hospitals in Maryland with a first MI between 1971-1972. Two controls were matched to each case. Controls were females from the same hospitals as cases, with no history of MI or abnormal Q waves on EKG, and matched by age and date of admission. Data were obtained from interviews and review of medical records,	39 cases (28% ever users), 81 controls	First MI	Ever users age-adjusted OR 0,8 (NS) risk-factor adjusted* OR 0,61 (0.20-1 .88) risk-factor adjusted* OR for surgical menopause only 0.37 (0.04-3,23) *adjusted for history of cardiovascular disease, smoking, educational level, and type of menopause

TABLE I-1: Postmenopausal Estrogen Use and Coronary Heart Disease Hospital-Based Case-Control Studies (page 3 of 3)

Author	Description of study	Number of study subjects	Measured endpoint	Relationship of hormonal replacement therapy to heart disease endpoints[ab]
La Vecchia (1987)	Cases were women less than 55 years of age admitted between January 1983 and December 1984 to the coronary care units of 30 hospitals in Northern Italy. Controls were matched to cases for index hospital and 5-year age group. Controls were admitted for acute conditions except cardiovascular, cancer, endocrine, gynecological, or primary diagnosis potentially related to cigarette smoking or hormone use. Data were gathered by trained interviewers.	168 cases, 100 pre-menopausal (5% current users) (3% past users); 251 controls	First MI	Current users: age-adjusted relative risk 1.85 (0.68-5.01) risk-factor adjusted* relative risk 2.95 (0.80-10.80) Past users: age-adjusted relative risk 1,01 (0.31-3.27) risk-factor adjusted* relative risk 0.77 (0.1 6-3.60) 'adjusted for multiple heart disease risk factors "No relation was evident with duration of use."

[a]Numbers in parentheses are 95 percent confidence intervals.
b Risk estimates are in terms of relative risk, unless otherwise specified,

KEY: AM I = acute myocardial infarction; EKG = electrocardiogram; ERT = estrogen replacement therapy; MI = myocardial infarction; NS = not statistically significant; OR = odds ratio.

SOURCE: Office of Technology Assessment, 1995.

percent) were smokers, which confounds interpretation of results. Also, the subjects were under 50 years of age, so the findings may not be generalizable to the overall population of postmenopausal women (14).

Population-Based Case-Control Studies

Among the seven population-based case-control studies of myocardial infarction and ERT, all but one demonstrated a trend toward decreased relative risk of myocardial infarction in estrogen users, although the results were statistically significant in only one of the studies that showed a trend toward decreased relative risk (92). (See table I-2.)

Population-based case-control studies differ from hospital-based case-control studies in that the cases and controls come from the community or a sample of the general population. Controls selected from the community rather than a hospital are likely to be more representative of the general population from which the cases were drawn than hospital-based case-control studies.

In one of the largest population-based case-control studies of myocardial infarction and estrogen use, Pfeffer and colleagues found among current users of estrogens an adjusted relative risk of 0.7 (0.3-1.4) for fatal and nonfatalMI(81). Estrogen use in this study was ascertained by review of pharmacy records. In a reanalysis of Pfeffer's data, Ross found that estrogen use among cases was underestimated, because one-third of the women who had estrogen usage noted on their medical records did not have records of estrogen prescriptions in the pharmacy records (92). The mean duration of use was less than three months, which would also bias the findings toward an underestimate because such a short duration is unlikely to be sufficient for a plausible biological effect (103).

Unlike the other case control studies in this group which used myocardial infarction as an endpoint, Thompson and colleagues used a combined endpoint of stroke and myocardial infarction (111). In that study, each of 603 women with stroke or myocardial infarction identified in 83 physicians' practices were matched with two controls from the same physician's practice and of the same age. Estrogen use was ascertained from medical records and patient interviews. Thompson showed a "weak" association between estrogen use and stroke and myocardial infarction, with a relative risk of 1.36 in estrogen users (95 percent confidence intervals 1.01 to 1.81). An association between estrogen use and decreased risk of coronary heart disease may have been obscured by combining the myocardial infarction endpoint with the endpoint of stroke.

Cohort Studies

The published results of 15 cohort studies all showed a reduced risk of coronary heart disease in estrogen users, although the results of one cohort study, the Framingham study, are equivocal.

Most cohort studies followed women with and without estrogen exposure, and thus had a control group internal to the study. In three studies, however, mortality in a cohort of estrogen users was compared with national mortality rates. These cohort studies without internal controls showed the lowest apparent relative risk of cardiovascular disease with estrogen use. (See table I-3.) But women who take estrogens are on average of higher socioeconomic status and more educated and therefore are probably healthier than the general population (19,103). Consequently, cohort studies without internal controls may overestimate the effect of estrogen exposure on cardiovascular disease.

The findings of cohort studies with internal controls, including the Framingham study, are summarized in table I-4. One of the largest cohort studies of cardiovascular disease risk among postmenopausal estrogen users is the Lipid Research Clinics Follow-up study, initiated by the National Heart, Lung, and Blood Institute in 1971 (12,15). Almost 2,300 women have been followed in this study. A 1987 report noted a statistically significant reduction in incidence of CHD or stroke death among current estrogen users (average length of use 8.5 years) compared with nonusers. The relative risk of cardiovascular death in estrogen users was 0.34. Adjustment for other potential

TABLE I-2: Postmenopausal Estrogen Use and Coronary Heart Disease—Community/Population-Based Case Control Studies (Page 1 of 5)

Author	Description of study	Number of study subjects	Measured endpoint	Relationship of hormonal replacement therapy to heart disease endpoints
Talbott (1 977)	Cases were white female residents of Allegheny County, Pennsylvania who had no prior recorded history of heart disease and who were ages 25 to 64 years old (mean age 55.6) when they died suddenly of atherosclerotic heart disease outside of the hospital between September 1973 and April 1975. Cases were identified from county coroner records and death certificates. Cases were matched to controls who were females living on the same block and who were within 10 years of patient's age. Information about cases was gathered from interviews of subjects' family and physicians. Information about controls was gathered from interviews of subjects.	64 cases (unknown number postmenopausal) (5% current users); 64 controls	Sudden death	Current users:[b] age-adjusted relative risk 0.34 (0.09-1 .30)
Pfeffer (1 978)	Cases and controls were women ages 50 to 98 years who were residents of a Southern California retirement community between 1964 and 1974. Cases had their first MI while in residence. Controls were drawn from a file containing all women in residence during the study interval. There were no black members of the population. Data was obtained from review of medical clinic and pharmacy records,	171 cases (30% ever users) (8.7% current users); 171 controls	First MI	Ever users: risk-factor adjusted* relative risk 0.86 (0.54-1 .37) current users: risk-factor adjusted* relative risk 0.68 (0.32-1 .42) *adjusted for age, hypertension, and diabetes
ROSS (1981)	Cases were women less than 80 years old living in a retirement community near Los Angeles who died of coronary heart disease between 1971 and 1975 inclusive. For each case a living and deceased female control were selected, matched for race, age, date of entry into the community, and, for deceased control, date of death. The deceased control was used to remove bias for extra medical attention the cases may have had toward the end of their lives Data was gathered from medical clinic records	133 cases (percent ever users not provided), 133 living controls; 133 deceased controls	Fatal coronary heart disease	Ever users. age-adjusted relative risk living controls: 0.43 (0.24-0.75) dead controls 0.57 (0.33-0.99) risk- factor adjusted* relative risk living controls. unchanged dead controls. unchanged *adjusted for multiple heart disease risk factors

TABLE I-2: Postmenopausal Estrogen Use and Coronary Heart Disease—Community/Population-Based Case Control Studies (Page 2 of 5)

Author	Description of study	Number of study subjects	Measured endpoint	Relationship of hormonal replacement therapy to heart disease endpoints
Bain (1981)	Cases were postmenopausal female nurses ages 30 to 55 in 1976 who reported hospitalization for MI. Twenty female nurses hospitalized in the same year with no history of MI were matched as controls to each case on the basis of year of birth and menopausal status at hospitalization. Information was gathered by questionnaire.	120 cases (53% ever users) (27% current users), 2,400 controls	First MI	Ever users. age-adjusted relative risk 0.9 (0.6-1.2) risk-factor adjusted* relative risk 0.8 (0.6-1 .3) current users. age-adjusted relative risk 0.7 (0,5- 1,1) risk-factor adjusted* relative risk 0.7 (0.4-1.1) age-adjusted relative risk in women with natural menopause 1,3 (0.5-3.4) age-adjusted relative risk in women with hysterectomy 1.0 (0,5-2,2) age-adjusted relative risk in women with hysterectomy and bilateral oophorectomy 0.4 (0.2-0.8) *adjusted for multiple heart disease risk factors
Adam (1981)	Cases were women ages 50 to 59 who died of MI in England and Wales during November 1978 identified from death certificates. Two controls matched by age to cases were randomly selected from the practice list of the general practitioner responsible for the care of the patient during life. Information was gathered from hospital records, postmortem reports, and questionnaires completed by the subject's general practitioner.	76 cases (12% ever users) (3% current users); 152 controls	Fatal MI	Ever users: unadjusted relative risk[b] 0.65 (0.29-1 .45) current users: unadjusted relative risk[b] 0.97 (0.41 -2.28)
Croft (1989)	A nested case-control was carried out on cohort data collected during the Royal College of General Practitioners' oral contraceptive study. Subjects were recruited by U.K. general practitioners, and were followed between May 1968 and July 1969. The cases were all women who had had their first AMI while under observation in the study. Controls were chosen from randomly selected general practice registers, matched for age to cases. Medical records were examined.	158 cases (9 estrogen users), 474 controls (32 estrogen users)	First MI	Ever users. unadjusted relative risk 0.8 (no c.i. provided) adjusted relative risk* 0.8 (0.3 to 1.8) *adjusted for social class, smoking, use of oral contraceptives, history of pre-eclampsia, hypertension, and hysterectomy

TABLE I-2: Postmenopausal Estrogen Use and Coronary Heart Disease—Community/Population-Based Case Control Studies (Page 3 of 5)

Author	Description of study	Number of study subjects	Measured endpoint	Relationship of hormonal replacement therapy to heart disease endpoints[a]
Beard (1989)	Cases were female residents of Rochester, Minnesota between 1960 and 1982 whose first manifestations of heart disease were sudden death or MI occurring between the ages of 40 and 59. Two controls matched by age to each case were selected from women seen at the Mayo Clinic. Information was obtained from review of medical records.	86 cases (27% ever users); 150 controls	MI or sudden death	Ever users: risk-factor adjusted* odds ratio 0.55 (0.24-1 .30) *adjusted for age, year, menopausal status, smoking, hypertension, and diabetes
Thompson (1989)	Cases were white women ages 45 to 69 who developed MI or stroke between 1981 to 1986 and whose general practitioners reported to Northwick Park Hospital, England. Controls were white female clinic patients matched for age and general practitioner. Information gathered from review of medical records and interviews.	603 cases (94% past users); 1,206 controls	MI and stroke	Ever users of estrogen alone, age-adjusted relative risk 1.12 (0.79-1 ,57) risk-factor adjusted* relative risk 1,09 (0,65-1 ,82) past users of estrogen alone: age-adjusted relative risk 0,86 (0.43-1 ,74) risk-factor adjusted* relative risk 1,16 (0.43-3.12) ever users of progestin alone. age-adjusted relative risk 1.90 (1,1 1 -3,25) risk-factor adjusted* relative risk 1.02 (0.45-2.32) ever users of combined estrogen -progestin: age-adjusted relative risk 0,86 (0,43-1 .74) risk-factor adjusted* relative risk 1.16 (0.43-3,12) *adjusted for marital status, smoking, history of hypertension venous thrombosis, stroke, MI, diabetes, and family history of MI

TABLE I-2: Postmenopausal Estrogen Use and Coronary Heart Disease—Community/Population-Based Case Control Studies (Page 4 of 5)

Author	Description of study	Number of study subjects	Measured endpoint	Relationship of hormonal replacement therapy to heart disease endpoints
Rosenberg (1993)	Cases were women, ages 45 to 69 (median age 60 years), who were residents of Massachusetts from 1986 until 1990. Controls were women, matched by metropolitan precinct and 5-year age group, with no prior history of MI, Ninety-eight percent of cases and 97 percent of controls were white. Data were gathered from interviews of physicians and patients,	858 cases (21% used unopposed estrogens, 3% used estrogen and progestins); 858 controls (21 % used unopposed estrogens, 3.5% used estrogens and progestins)	First MI	Ever users. risk-factor adjusted* relative risk 0.9 (0.7-1 .2) recent users: risk-factor adjusted* relative risk 0.8 (0.4-1 .3) past users: risk-factor adjusted* relative risk 0.9 (0.7-1 .3) unopposed estrogen users: risk-factor adjusted relative risk 1.3 (0.4-4.9) estrogen and progestin users: risk-factor adjusted relative risk 1.2 (0.6-2.4) progestin only users: risk-factor adjusted relative risk 1.3 (0.4-4.9)

*adjusted for multiple heart disease risk factors The estimated relative risk decreased with increased duration of unopposed estrogen use to 06 (O 4-1 1) (test for trend p= 0.08), The association of decreased risk with duration of use was stronger with recent use (test for trend p< O 05) than for past use (test for trend P=O. 86)

TABLE I-2: Postmenopausal Estrogen Use and Coronary Heart Disease—Community/Population-Based Case Control Studies (Page 5 of 5)

Author	Description of study	Number of study subjects	Measured endpoint	Relationship of hormonal replacement therapy to heart disease endpoints
Mann (1994)	Cases and controls were women ages 45 to 64 years who were included in the general practice files of the VAMP database of the British National Health Service beginning in June 1987 to May 1993. Cases comprised all incidents of both fatal and non-fatal cases of MI where there were records of HRT prescriptions within 6 months of the date of the MI. Controls were females in the same age group with no prior history of MI. Four controls were matched to each case. Data was gathered from computerized medical records.	1,521 cases (7.7% ever users); 6,084 controls (9.2% ever users)	MI	Ever users. age-adjusted odds ratio 0.82 (0.67-1 .01) risk-factor adjusted* odds ratio 0.83 (0.66-1 .03) age-adjusted odds ratio for estrogen-progestin 0.68 (0.47-0.97) age-adjusted odds ratio for unopposed estrogen 0.93 (0.47-1 .86) *adjusted for history of smoking, diabetes, hypertension, hysterectomy, and hyperlipidemia

[a]95 percent confidence intervals are reported after risk estimates.
b Figure obtained from reanalysis of data in original paper, included in meta-analysis by M.J. Stampfer, and G. A. Colditz,"Estrogen Replacement Therapy and Coronary Heart Disease A Quantitative Assessment of the Epidemiological Evidence," Preventive Medicine 20:47-63, 1991
KEY' AM I = acute myocardial infarction; c.i. = confidence interval; HRT = hormonal replacement therapy; MI = myocardial Infarction.

SOURCE: Office of Technology Assessment, 1995

TABLE I–3: Postmenopausal Estrogen Use and Coronary Heart Disease Cohort Studies Without Internal Controls (Page 1 of 2)

Author	Description of study	Number of study subjects	Measured endpoint	Relationship of hormonal replacement therapy to heart disease endpoints[a,b]
Byrd (1977)	Cohort included women mean age 44 years, who received hysterectomies from one Nashville, TN, gynecologist from the late 1940s to 1977. All cohort members received postmenopausal ERT (typically 1.5 mg CEE per day), and were followed for at least 5 years (average duration of followup was 14,3 years). The women were followed up by personal contacts, office visits, and questionnaires. Expected rates of fatal heart disease were obtained from the report of the Division of Vital Statistics, Tennessee Department of Public Health.	1,016 women (all estrogen users); 13 cases of fatal CHD	Fatal CHD	Ever users: unadjusted relative risk[c] 0,37 (p<o.oo5)
MacMahon (1978)	Followup of study by Hoover, et al. (1976) originally assembled for the evaluation of cancer risk, to include mortality from all causes. The medical records of all white women seen in one private practice in Louisville, KY, from 1939 to 1972, were reviewed, Average age of women in the cohort at baseline was 49 years. Mean duration of followup was 12 years, Rates of fatal CHD in the cohort were compared to the age-specific death rates in the general population.	1,891 women (all estrogen users); 33 cases of fatal CHD	Fatal CHD	Current users: age-adjusted relative risk 0.30 (0.21 -0,42)
Hunt (1990)	Cohort included women receiving HRT recruited between 1977 and 1982 from 21 menopause clinics around Britain. Subjects were followed through 1988 and median duration of followup was 8.0 years. Sixty-three percent of cohort was 45 to 54 years of age upon entry into cohort. Mortality rates in the cohort were compared to the expected rates in the female population of England and Wales. Information about deaths was obtained through death registries, and diagnosis was confirmed by review of medical records.	4,544 women (2,726 postmenopausal) (all HRT users) (43% estrogen-progestin users); 36 cases of fatal IHD	Fatal IHD	Ever users: age-adjusted relative risk 0.41 (0.20-0.61)

TABLE I–3: Postmenopausal Estrogen Use and Coronary Heart Disease Cohort Studies Without Internal Controls (Page 2 of 2)

Author	Description of study	Number of study subjects	Measured endpoint	Relationship of hormonal replacement therapy to heart disease endpoints[a,b]
Falkeborn (1992)	Cohort comprised 23,174 women aged 35 and older (median age 54 at study entry) from the Uppsala Health Care Region of Sweden, who had been treated with estrogen/progestin. Subjects were identified from pharmacy records as having been prescribed non-contraceptive estrogens from 1977 to 1983, Subjects were followed for an average of 5.8 years. Cases of MI within cohort were identified through a regional hospital inpatient registry. A subcohort of 735 women were surveyed in 1980 and 1984 by mailed questionnaire to further characterize the cohort with respect to lifetime hormone exposure and the presence of other risk factors. The incidence of first MI in the cohort was compared with that in the general population.	23,174 women (all HRT users, 21% current users), 227 cases of first MI	First MI	Ever users. age-adjusted relative risk estradiol/ conjugated estrogens 0.74 (0.61 -0.88) other estrogens only 0.90 (0.74-1 .08) estrogen/progestin combination 0.50 (0.28-0.80) overall age-adjusted relative risk 0,81 (0.71 -0.92) "The relative risk tended to decrease with increased duration of followup, " from a relative risk of 0,96 (0,44-1 .83) during the first year to a relative risk of 0.76 (0.55-1 .02) during the last (6 years later).

KEY: CHD = coronary heart disease, IHD = ischemic heart disease, MI = myocardial infarction

[a] Estimates are of relative risk unless otherwise specified
b 95% confidence intervals are provided in parentheses.

C Figures obtained from reanalysis of data in text. Reanalysis of data was presented in M J Stampfer, and G A Colditz, "Estrogen Replacement Therapy and Coronary Heart Disease A Quantitative Assessment of the Epidemiological Evidence," Preventive Medicine 2047-63, 1991

SOURCE Off Ice of Technology Assessment, 1995

TABLE I–4: Postmenopausal Estrogen Use and Coronary Heart Disease—Cohort Studies with Internal Controls
(Page 1 of 5)

Author	Description of study	Number of study subjects	Measured endpoint	Relationship of hormonal replacement therapy to heart disease endpoints[a]
Hammond (1979)	Study subjects were identified through Duke University Medical Center's (Durham, NC) inpatient medical record retrieval system and outpatient office records. All cohort subjects received diagnoses related to hypoestrogenism between 1940 and 1964, who returned for followup for five or more years after diagnosis, and had most recently been seen at Duke after January 1, 1974. Patients referred to Duke were excluded from the sample. Mean age of subjects was 46.3 years at baseline.	610 women (49% estrogen users); 58 cases	CHD	Ever users: unadjusted odds ratio[b] 0.33 (0.1 9-0.56)
Lafferty (1985)	The cohort was recruited from 173 private practice patients of the author for a prospective study between 1966-1981, Candidates had been followed for not less than 3 years and had periodic physical exams and laboratory studies. The mean duration of followup was 1.6 years. The mean age of subjects was 53,7 years (range 45 to 60 years) at baseline.	124 women (49% estrogen users); 7 cases	MI	Ever users: unadjusted odds ratio[b] 0.17 (0.03-1 .06)
Wilson (1985)	Patients considered for inclusion were members of the Framingham (Massachusetts) Heart Study cohort who participated in the 12th biennial exam (index) between 1970 and 1972 and who were postmenopausal and over 50 years of age at that exam. The cohort was followed for 8 years.	1,234 women (14Y0 past users of estrogen, 1O% current users); 194 cases of CVD, 48 cases of CVD death, and 51 cases of MI	All CVD	Ever users: relative risk for all CVD 1,76 (p< O.01) adjusted for age and HDL level; relative risk for CVD death 1.94(p<0.05) adjusted for age and HDL level; relative risk for MI 1.87(p<0.05) adjusted for age and HDL level

TABLE I–4: Postmenopausal Estrogen Use and Coronary Heart Disease—Cohort Studies with Internal Controls (Page 2 of 5)

Author	Description of study	Number of study subjects	Measured endpoint	Relationship of hormonal replacement therapy to heart disease endpoints
Eaker (1987)	The author reanalyzed the data from the cohort of the Framingham (Massachusetts) Heart Study, described above (Wilson, 1985).The subjects included women in the Framingham Study cohort who were 50-59 years of age or 60-69 years of age upon exam 1 in 1950, exam 6 in 1960, or exam 11 in 1970. The cohort was divided on the basis of the subject's age at exam. Duration of followup was 10 years.	1,297 women (14% past users, 10% current users) 695 women ages 50 to 59; 35 cases 602 women ages 60 to 69; 51 cases	CHD except angina	50-59 years of age: relative risk 0.26 (0.06-1 .22) adjusted for age and HDL level relative risk 0.4 (p< O.05)adjusted for multiple risk-factors including HDL level 50-69 years of age: relative risk 1.68 (0.71 -4.00) adjusted for age and HDL level relative risk 2.2 (p< O.05) adjusted for multiple risk-factors, including HDL level
Bush (1987a)	The cohort consisted of 2,270 white women, ages 40 to 69 at baseline, who were followed for an average of 8.5 years. All women included in the study were participants in the Lipid Research Clinic (LRC) Prevalence Study of CVD, that was conducted in 10 North American clinics between 1972 and 1976. Study was restricted to whites due to the small number of minorities in the LRC study.	2,270 women (26% ever estrogen users); 50 cases	Fatal CVD	Ever users: age-adjusted relative risk 0.34 (0.12-0.81) risk-factor adjusted relative risk 0,37 (0.16-0.88)
Pettiti (1987)	The cohort included women aged 18 to 54 during December 1968 through February 1972 who participated in the Walnut Creek Contraceptive Drug Study who never used any type of estrogens or used estrogens for reasons other than contraception. Duration of followup was 10 to 13 years.	6,093 women (44% ever users); 40 cases of AM I	Fatal CVD or fatal MI	Ever users: age-adjusted relative risk 0.9 (0.2-3.3) for fatal CVD risk-factor adjusted relative risk 0.61 (0.3-1 .1) for fatal CVD age-adjusted relative risk 0.3 (0.1 -1 .3) for fatal MI
Criqui (1988)	Study subjects were followed between 1972 to 1986 when they participated in a community survey of homogeneous, white, upper-middle class residents of a planned, small Southern California retirement community (Rancho Bernardo). Women were 50 to 79 years of age at baseline. Average duration of followup was 12 years.	1,868 women (39% ever users), 87 cases	Fatal CHD	Ever users: age-adjusted relative risk 0.75 (0.45-1 24) risk-factor adjusted relative risk 0.99 (0.59-1 .67)

TABLE I–4: Postmenopausal Estrogen Use and Coronary Heart Disease—Cohort Studies with Internal Controls (Page 3 of 5)

Author	Description of study	Number of study subjects	Measured endpoint	Relationship of hormonal replacement therapy to heart disease endpoints
Avila (1 990)	The study cohort comprised all female members of the Group Health Cooperative of Puget Sound who were ages 50 to 64 years upon entry to cohort between 1978 to 1984. Cases were selected from women who were hospitalized and later discharged with a first occurrence of MI. Average duration of followup was 5 years.	24,900 women (14% current users), 120 cases	MI	Current users, age-adjusted relative risk 0.07 (0.4-1 .3) risk-factor adjusted relative risk 0,7 (0.4-1 .4)
Henderson (1991)	The cohort comprised female residents of Leisure World Retirement Community, Laguna Hills, California, who responded to a health questionnaire. The cohort was followed for 7.5 years using death certificate records of the local health department. Female residents were almost uniformly white, moderately affluent, and well educated with a median age of 73 years.	8,853 women (41% past users, 17.3% current users), 203 cases	Fatal AM I or fatal IHD	Current users: age-adjusted relative risk 0.601 (p< O.001) for fatal AMI age-adjusted relative risk of 0.79 (NS) for IHD Duration (for a fatal AM I): <3 years: 0.64 (p<0.05) 4-14 years: 0.60 (p<0.05) >15 years: 0.52 (p<O.O1) There was a significant trend toward decreased risk with increased duration of use for both IHD and AMI. Recency (years since last use) for fatal AMI. >15 years, 0,73 (NS) 2-14 years. 0.47 (p<O.01) O-1 year. 0.51 (p< O.05) There was a significant trend toward decreased risk of both AMI and IHD with increased recency of use,

TABLE I–4: Postmenopausal Estrogen Use and Coronary Heart Disease—Cohort Studies with Internal Controls (Page 4 of 5)

Author	Description of study	Number of study subjects	Measured endpoint	Relationship of hormonal replacement therapy to heart disease endpoints[a]
Stampfer (1 991)	The cohort includes participants in the Nurses Health Study. The study cohort began in 1976 when 121,700 female married registered nurses in 11 large states completed questionnaires about their medical histories and postmenopausal hormone use. Followup questionnaires were mailed at two year intervals thereafter. The study population includes participants ages 30 to 55 at baseline who had no preexisting cancers or CVD history that could be associated with hormone use. Mean duration of followup was 7 years.	48,470 female registered nurses (21.8% current estrogen users; 25.2% past users), 405 cases	Nonfatal MI and fatal CHD	Current users. age-adjusted relative risk 0.51 (0.37-0.70) risk-factor adjusted relative risk 0.56 (0.40-0.80) Past users: age adjusted relative risk 0,91 (0.73-1 .14) risk-factor adjusted relative risk 0.83 (0.65-1 .05) Ever users: risk-factor adjusted relative risk 0.72 (0.55-0.95) There were no significant trends with regard to duration of use or recency of use (time since last use).
wolf (1 991)	This cohort consists of a natural sample of women from the National Health and Nutrition Examination (NHANES) followup study who were at least 55 years of age and menopausal at baseline survey between 1971 and 1975. The study was restricted to white female participants. Followup occurred from 1982 to 1984, and again in 1986 and 1987. Followup intervals ranged from 11,4 -16.3 years (mean 14.1 years) for survivors and 2 months to 16,3 years (mean 8.6 years) for the descendants. Women were categorized as either ever users or never users of HRT on the basis of their response to the 1982-1984 followup questionnaire. HRT type was almost exclusively conjugated equine estrogens (Premarin). Mean age at baseline exam was 65.7 years.	1,944 women (21 % ever users); 347 cases	Fatal CVD	Ever users: risk-factor adjusted relative risk 0.66 (0.48-0.90)

TABLE I–4: Postmenopausal Estrogen Use and Coronary Heart Disease—Cohort Studies with Internal Controls °
(Page 5 of 5)

Author	Description of study	Number of study subjects	Measured endpoint	Relationship of hormonal replacement therapy to heart disease endpoints[a]
Manolio (1 993)	Cardiovascular Health Study participants were recruited from a random sample of Health Care Financing Administration Medicare eligibility lists in 4 U.S. communities: Forsyth Co., NC; Sacramento, CA, Washington Co., MD; and Allegheny Co., PA. The participants were females from 65 to 100 years of age with a mean age of 72.4 years.	Cases, 461 12% current users 39% ever users cohort size, 2,955 39% post menopausal	Definite CHD	Ever versus never users[a] age adjusted relative risk P = 0.4

KEY: AMI = acute myocardial infarction, CHD = coronary heart disease, CVD = cardiovascular disease, ERT = estrogen replacement therapy, HDL = high-density lipoprotein cholesterol, IHD = ischemic heart disease, MI = myocardial infarction

[a] Ninety-five percent confidence intervals are provided in parentheses, unless otherwise specified
b Estimates of crude odds ratio derived from reanalysis of data in the text or from meta-analysis by Stampfer and Colditz in M J, Stampfer and G.A Colditz, "Estrogen Replacement Therapy and Coronary Heart Disease' A Quantitative Assessment of the Epidemiological Evidence, " *Preventive Medicine 20:47-63, 1991*

SOURCE: Office of Technology Assessment, 1995.

confounding factors (age, blood pressure, and smoking) did not substantially change the finding of a reduction in risk of cardiovascular death among current estrogen users.

On the basis of multivariate analysis of the results of this study, the investigators concluded that the beneficial effect of estrogens on cardiovascular disease risk was substantially mediated through HDL levels. When the multivariate analysis included HDL, the benefit of cardiovascular disease mortality among estrogen users compared with nonusers was reduced and no longer statistically significant, a finding consistent with the hypothesis that the protective effect of estrogens is substantially mediated through increased HDL levels. Preliminary data from the 15-year follow up of patients in the study demonstrated a 65-percent reduction in cardiovascular disease and an approximately 50-percent reduction in all-cause mortality (28). Even after adjusting for age, HDL, and LDL, estrogen users continued to have a risk of 60 percent that of nonusers.

A nationwide study of nurses also found postmenopausal estrogens to have a protective effect on major coronary disease (102). The Nurses' Health Study was established in 1976 with 121,700 female nurses ages 30 to 55 years old. By 1986,48,470 of these women were postmenopausal. Participants who reported ever using estrogens in the past had a statistically significant relative risk for nonfatal and fatal coronary heart disease of 0.51 after an average of 7 years' follow-up. Adjustments for a variety of cardiac risk factors including high cholesterol, family history of heart disease, hypertension, diabetes, obesity, and smoking did not substantially change these relative risk estimates.

In an ongoing prospective study in a retirement community near Los Angeles (Leisure World), Henderson and colleagues found that women who used ERT had a relative risk of fatal acute MI of 0.60 compared with nonusers (39). This study was begun in 1981 to investigate the risks and benefits of menopausal ERT. A questionnaire was mailed to all 20,000 residents of this retirement community in 1981, and the two-thirds who completed and returned the questionnaire became members of the study cohort. About 9,000 of these were women (77). After 7.5 years of followup, current users had an age-adjusted relative risk of fatal ischemic heart disease of 0.46 compared with nonusers. Adjustment for several CHD risk factors did not substantially change the results. Henderson also found that the overall mortality rate in those who had ever used estrogen was 20 percent lower than lifetime nonusers (95 percent confidence intervals 0.7 to 0.87) and the overall mortality in current users of estrogen with more than 15 years of estrogen use was 36 percent below that in nonusers (95 percent confidence intervals 0.51 to 0.82) (39).

A cohort of 6,093 women ages 18 to 54 from the Kaiser Permanence Medical Program was followed for an average of 10 to 13 years (80). The mortality rate from heart disease and stroke was slightly lower among estrogen users, with a relative risk of 0.9 (95 percent confidence intervals 0.2 to 3.3). After adjustment for a variety of cardiovascular risk factors, including age, hypertension, obesity, and smoking, the apparent benefit was more marked, with a relative risk of 0.6 but the reduction in risk remained statistically insignificant (95 percent confidence intervals 0.3 to 1.1).

In contrast to the other cohort studies, the Framingham Heart Study[3] reported a 50 percent increased risk for all circulatory disorders in postmenopausal estrogen users (120). An increased incidence of MI was observed among estrogen users, particularly those who smoked cigarettes.

One criticism of the Framingham study's conclusions with respect to postmenopausal ERT and

3 The Framingham Heart Study, named for the Boston suburb where residents have participated since 1948, began with 5,209 healthy men and women ages 30 to 62. In 1971, the ongoing study was expanded to include the offspring of the original participants. The effects on diet, medication, and life-style on health have been assessed every two years (biennial examinations).

cardiovascular disease is that a reduction in cardiovascular disease risk in estrogen users may have been obscured by including in the estrogen user group women whose use was remote; in the Framingham study, anyone who had used estrogen at some time in the eight years before the twelfth biennial examination was counted as an estrogen user (119).

Another criticism of the Framingham study is that the investigators adjusted the results for HDL levels. Because estrogen's beneficial effects are thought to be substantially mediated through its effect on HDL level (15), the analysis may have underestimated the cardiovascular benefits of postmenopausal ERT.

The Framingham study has also been criticized for the use of subjective measures of cardiovascular disease (29). In the Framingham study, the relative risk of cardiovascular disease was estimated using a number of endpoints including angina pectoris (chest pain due to inadequate oxygenation of the heart), coronary heart disease, intermittent claudication (symptom associated with atherosclerosis and other occlusive arterial diseases characterized by leg pain with walking and relieved by rest), transient ischemic attack (occlusive vascular disease symptom characterized by brief periods of cerebral dysfunction, with no persistent necrologic deficit), myocardial infarction, congestive heart failure, coronary heart disease death, and sudden death. Chest pain can be due to a wide variety of causes, some of which can be mistakenly attributed to the presence of coronary heart disease. In a reanalysis of the Framingham data, excluding the nonspecific endpoint of angina pectoris, Eaker demonstrated a statistically nonsignificant reduction in risk of coronary heart disease among younger estrogen users (relative risk 0.4,95 percent confidence interval 0.1 to 2.3) and a statistically nonsignificant increase in risk of coronary heart disease among older estrogen users (relative risk 1.8, 95 percent confidence interval 0.5 to 6.9).

Although prospective cohort studies have important advantages over case-control studies in avoiding bias from the subject recall of exposure and the difficulties in selection of controls, a problem with some cohort studies is that estrogen use was often ascertained only at the initiation of the observation period and not reascertained at a later point in the study (103). By failing to update estrogen use status, current and former users may be misclassified, and an underestimate of the effect of estrogen may result, particularly because the benefits of estrogen use are most pronounced among current or recent users.

Cross-Sectional Studies

Recently, a number of cross-sectional surveys of estrogen use in women who have had coronary angiography (heart catheterization) have been reported; these studies have found reduced incidence of CHD in estrogen users (table I-5). Angiographically demonstrated coronary artery obstruction is thought to be a more specific endpoint for the presence of CHD than signs and symptoms such as angina pectoris or MI. Coronary angiography involves the injection of x-ray opaque dye into each artery of the heart (78). X-ray images of the heart (cineangiograms) are recorded, and these images are then reviewed by the cardiologist for evidence of obstructions of the coronary arteries.

Cross-sectional studies are a subcategory of case-control studies where the presence of disease and the exposure to the agent are ascertained simultaneously (94). In the studies listed in table I-5, the presence of angiographically demonstrated coronary artery obstruction and the patient's history of estrogen exposure were simultaneously ascertained. These studies have found reduced disease in women who had taken estrogen. For example, Gruchow et al. reports on a series of 933 women ages 50 to 75 years who underwent coronary angiography (36). Estrogen users were one-half as likely as nonusers to have moderate or severe occlusion of the coronary arteries. In nonusers, the likelihood of occlusion increased with age, whereas in users, no age trend was evident.

Hong et al. reported on a series of 90 consecutive women 55 years old or older undergoing diagnostic coronary angiography (41). Only 22

percent of estrogen users had significant obstruction of a major coronary artery (defined as 25 percent or more luminal diameter narrowing), whereas 68 percent of nonusers had significant obstruction.

Randomized Clinical Trials

In the only prospective randomized double-blind clinical trial of estrogen use and heart disease, Nachtigall and colleagues reported on the 10-year followup of eighty-four pairs of chronically ill women in a long-term-care hospital matched for age and diagnosis, who were randomly assigned to take estrogen opposed with progestin (PERT) or placebo (73). PERT users had a lower relative risk of myocardial infarction than nonusers, but there were only four myocardial infarctions in the study and the difference in risk was not statistically significant. In a study this small, however, one would expect only very large differences in relative risk of disease to be capable of producing statistically significant results.

Some investigators have argued that much of the reported heart disease benefit of HRT may be due to "healthy user" bias—the selection of relatively healthy women with a lower risk of heart disease for HRT. These investigators argue that estrogen users are generally of higher social class than nonusers (8), and social class is inversely associated with both heart disease and cancer (51,65). They also argue that the lower heart disease incidence in ERT users maybe because doctors were reluctant to prescribe estrogens to women with coronary risk factors 10 years ago, because, at that time, estrogen was contraindicated in these women because earlier studies had found increased risk of thrombosis and heart attack in young women taking oral contraceptives and in older men treated with estrogen.

One investigator showed that cohort studies that found a reduction of heart disease incidence in ERT users also showed a reduction in risk of total cancer incidence in ERT users, even though ERT would not be expected to have a beneficial effect on total cancer incidence (83).

Estrogen replacement therapy, however, has been found to prolong survival even in women who are not "healthy" women who already have significant coronary artery disease. Recent studies have compared the later survival of estrogen users versus nonusers with previously documented coronary artery lesions demonstrated by arteriography. Sullivan et al. recently found all-cause mortality over a 10-year period to be lower in women with coronary artery disease who used ERT than in those who never used estrogen (1 07). They reported a retrospective analysis of postmenopausal estrogen use, coronary artery obstruction (stenosis), and survival in 2,268 women 55 years or older who underwent coronary arteriography in the past. They compared overall survival in estrogen users and nonusers who initially had various degrees of coronary artery obstruction as demonstrated by arteriography. Over 10 years of followup, there was no difference in survival between estrogen users and nonusers with no initial evidence of coronary artery obstruction on arteriography. But in those with initially mild to moderate coronary artery occlusion (less than 70 percent stenosis), 10-year survival was 85 percent in never users versus 95.6 percent in ever users of estrogen. And in those who initially had severe occlusion (70 percent or greater stenosis), survival was 60 percent among those who never used estrogen and 97 percent among those who had ever used estrogen. One implication of these findings is that ERT may have beneficial effects on the heart even when started in older women with preexisting coronary heart disease.

Barrett-Connor found that, even within a group of women from the same socioeconomic class, women taking estrogen were different from nonusers with regard to health promotion and disease prevention measures (6). In order to minimize the bias introduced by differences in socioeconomic status between estrogen users and nonusers, Barrett-Connor evaluated the estrogen use patterns of 1,057 postmenopausal women from the same socioeconomically upper-middle-class community in California (6). The women were categorized as

never users, past users, and current users. After an average followup period of 4.4 years, 95 percent of these women completed a mailed health survey questionnaire that asked about lifestyle and health care factors related to good health. In general, women who never used estrogen were least likely to have implemented healthy behavior changes, and were least likely to have had screening evaluations. Seventy percent of the group of current estrogen users had had a mammogram in the last 12 months, whereas 45 percent of the never users had had one ($p < 0.001$).

Other investigators have also argued that users of ERT are relatively compliant, and that "compliance bias" may account for some of the apparent benefit of ERT on heart disease (79). To examine the magnitude of "compliance bias," analyses of data from two randomized clinical trials of drug treatments for heart disease have examined total mortality in persons who complied with the taking of placebo (24,43). In these analyses, subjects who complied with the taking of a placebo had significantly lower overall mortality. The benefit of compliance with placebo was not reduced by adjustment for a large number of variables, both medical and sociodemographic, that might affect mortality.

The issue of selection bias will not be completely resolved until completion of randomized controlled clinical trials of HRT and heart disease. A number of randomized controlled clinical trials have been performed that have examined the effect of HRT on lipids and lipoproteins. In women, levels of high density lipoprotein (HDL) and triglycerides, and to a lesser extent, low density lipoproteins (LDL) predict cardiovascular death in women (9). These studies have demonstrated that ERT, and to a lesser extent, PERT, have induced favorable changes in lipids and lipoproteins, consistent with a reduced risk of heart disease in HRT users.

A controlled clinical trial that uses the endpoint of coronary heart disease symptoms or mortality would be expensive because of the large number of study participants and the long duration of followup that would be required (71). Therefore, many trials have been conducted that measure estrogen's effect on various intermediate endpoints for coronary heart disease, such as blood lipid and lipoprotein levels. The first long-term large-scale controlled clinical trial of HRT using coronary heart disease endpoints was begun in fall 1993 as part of the Women's Health Initiative. This 15-year, $625 million study, sponsored by the National Institutes of Health, will examine the effect of HRT, as well as low fat diets, calcium supplements, and vitamin D supplements on the incidence of heart disease, osteoporosis, and other diseases. The study includes a clinical trial involving 57,000 women ages 50 to 79, and an observational study involving 100,000 women from 45 medical centers across the United States.

Randomized controlled clinical trials examining the effect of estrogen on heart disease risk factors have shown evidence of heart disease benefits in users of estrogen. The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial involved 875 women, 45 to 64 years old at study entry, who were randomly assigned to either estrogen, one of three estrogen/progestin combinations, or placebo (122). During this three-year multicenter trial, the women were monitored for changes in a number of heart disease risk factors, including blood pressure LDL, HDL, and hemostatic factors. At the end of the three year trial period, women taking estrogen alone had significant increases in HDL, decreases in LDL, and decreased fibrinogen levels changes consistent with a decreased risk of heart disease in estrogen users.

EVIDENCE ON PERT AND CHD

The primary indication for adding progestins to the HRT regime is to reduce the risk of estrogen-induced irregular bleeding, endometrial hyperplasia (abnormal overgrowth of the inner lining of the uterus, or endometrium), and endometrial cancer (118). (See appendix G for more discussion.) But an important unresolved issue is whether the benefits of PERT in protecting the endometrium are outweighed by the effect of progestins on the risk of coronary artery disease. Studies of the relationship of HRT to coronary artery disease have been largely limited to ERT. The effect of proges-

tin supplementation has not been extensively evaluated because the routine addition of progestins to prevent estrogen-induced endometrial carcinoma has been recommended only recently (66).

Progestins are suspected to have an adverse impact on cardiovascular disease risk because progestins have opposite effects on lipid and lipoprotein metabolism from estrogens (84). Progestins decrease HDL levels (40,76,99). Different types of progestins, however, vary in their impact on lipids and lipoproteins, with the more androgenic progestins, particularly those derived from the male hormone testosterone, having a greater adverse impact. For example, Hirvonen et al. found that the progestins levonorgestrel and norethindrone in large doses (up to 10 mg) substantially reduced HDL, and the less androgenic progestin medroxyprogesterone acetate (10 mg) also reduced HDL levels, but not to as great an extent (40). Ottosson found that medroxyprogesterone acetate lowered HDL-2 cholesterol level, negating the increase observed with oral estrogens (76). Some evidence suggests that progestins may also adversely affect vessel-wall physiology (62).

There is some evidence that lower doses of the less androgenic progestins are sufficient to induce endometrial transformation and not substantially attenuate estrogen's beneficial effect on lipoproteins (2,34,45,49, 100,113,116,1 17,123) and other metabolic changes associated with heart disease risk (69,97). Progestin's effect on lipoproteins appears to be dose dependent, and lower doses of progestins may not substantially reduce estrogen's beneficial effect on HDL (45).

Nabulsi and colleagues found in a cross-sectional analysis of postmenopausal women that the addition of progestins did not attenuate estrogen's beneficial effects on heart disease risk factors; users of estrogen with progestin actually had a better profile of heart disease risk factors than users of estrogen alone (72). The investigators examined heart disease risk factors among 4,958 postmenopausal women, ages 45 to 64, from four regions of the United States, who were participating in the Atherosclerosis Risk in Communities study. They examined the associations of HRT with blood pressure, concentrations of plasma lipids and hemostatic factors, and fasting serum concentrations of glucose and insulin. Approximately 63 percent of the women had never used HRT, 16 percent had formerly used HRT, and 21 percent currently used HRT. Among current users of HRT, 83 percent were using estrogen alone (primarily conjugated equine estrogens (CEE)), and 17 percent were using PERT (primarily CEE with low dose medroxyprogesterone acetate).

The investigators found that, after adjusting for differences in other heart disease risk factors, current users of estrogen had significantly increased levels of HDL and decreased levels of LDL than did nonusers (72). They also found no significant difference in levels of HDL and LDL between users of ERT and users of PERT. Users of ERT had significantly higher plasma triglyceride levels than users of PERT. As elevated triglyceride levels are thought to increase heart disease risk, users of estrogen alone had a somewhat poorer plasma lipid profile than users of estrogen with progestin, but both groups of current users had better lipid profiles than nonusers. Finally, current HRT users had significantly lower levels of lipoprotein(a) than nonusers, with users of PERT having significantly lower levels of lipoprotein(a) than users of estrogen alone. Lipoprotein(a) concentrations may be inversely related to heart disease risk (98). Other changes were observed in the two groups of current users that would be predicted to lower the risk of coronary artery disease: a decline in fibrinogen levels (a serum protein involved in coagulation) and a decrease in glucose and insulin levels. Users of ERT had higher levels of coagulation factor VII and protein C than users of PERT and nonusers. This would suggest that PERT would have a better hemostatic profile than ERT.

These findings confirm three other population-based studies in which HDL levels in women who received ERT were similar to those in women who received PERT (8,32,1 14).

Recently, Falkeborn et al. reported the results of a study of first MI among a cohort of 23,174 postmenopausal estrogen/progestin users compared with postmenopausal women in the community (31). They found an age-adjusted relative

risk of first MI among current users of CEE (or estradiol) with progestin of 0.74 (0.61 to 0.81).

Results from the PEPI trial have also shown evidence of heart disease benefits in users of PERT, although the benefits are not as great as those in users of ERT (122). At the end of the three year trial period, women taking estrogen plus a synthetic progestin (medroxy progesterone) had a 2 milligram per deciliter (mg/dL) increase in HDL, whereas users of estrogen alone or estrogen plus a natural progestin (micronized progesterone, available in Europe) had about a 6 milligram per deciliter (mg/dL) increase in HDL, and the women assigned to the placebo group experienced no increase in HDL. Both the ERT group and the PERT group had significantly lower LDL than the placebo group. Both treatment groups experienced improvements in hemostatic factors and no change in blood pressure compared with the placebo group.

CONCLUSIONS

The conclusion of authors of several recent reviews of the evidence is that ERT reduces the risk of coronary heart disease (30,38,59). Both Stampfer and Bush, in recent meta-analyses of the data, concluded that the evidence strongly suggests that women taking estrogen therapy are at a risk for coronary heart disease about half that of nonusers (13,102). Several authors have found that the consistency of findings is stronger in the better designed and analyzed studies (13,56,59,84,93, 102).

Several studies demonstrated that women who currently use estrogen (current users) had a lower risk of coronary heart disease than women who had used them in the past (past users) (4,39, 64,81,88,90,91,102,111). Few data are available about whether dose, length of use, and type of estrogen affect risk. One study that examined the effect of estrogen duration on CHD risk failed to detect any effect of duration (102). However, Henderson et al. showed that women with a history of use showed a decrease in relative risk of fatal acute MI and fatal ischemic heart disease with increased duration of use (39). Rosenberg et al., in a case-control study, also found a significant trend toward decreased risk of first MI with increased duration of use of HRT, but only among current users (90).

Studies that examined dose failed to demonstrate a decreased risk of coronary heart disease with greater doses (39,102). But Ross found a nonsignificant trend toward decreased risk with higher doses of conjugated equine estrogens (92). Studies have not examined whether there are differences in efficacy with different estrogen preparations. Further study is needed on whether dose, length of use, and type of estrogen used affect risk.

There is evidence that HRT's heart disease benefits will continue into women's later years. Epidemiologic studies have demonstrated HRT's heart disease benefits in elderly women (15,39, 88,107,108).

OTA's review of the evidence concurs with those of other reviewers: there is both a theoretical rationale and empirical evidence to support a reduced risk of heart disease in women who use estrogens.

OTA chose a relative risk of 0.5 as the base case estimate of heart disease risk in current users of estrogen. In formulating this estimate, OTA placed greater emphasis on cohort studies than case-control studies, because cohort studies are less prone to bias. In general, cohort studies have demonstrated a greater heart protective effect of ERT than case control studies. Among cohort studies, 10 of 17 estimated relative risks of heart disease of 0.5 or below, and 13 of 17 were consistent with the hypothesis that ERT reduces heart disease risk in current users by half (confidence intervals included **0.5).**[4] The major disadvantage of cohort studies without internal controls is that the "control" group may not be comparable to the clinic

4 0TA relied on the results of the **Framingham** cohort published by Eaker (29), because the results of the major paper on heart disease in the Framingham cohort did not report the crude or age-adjusted cardiovascular disease rates.

TABLE I–5: Cross–Sectional Surveys of Coronary Artery Occlusion Among Women With and Without Postmenopausal Estrogen Who had Coronary Angiography

Study	Patient's age	Number of patients	Type of estrogen use	Percentage of estrogen users	Age-adjusted relative risk[a]	Risk–factor adjusted relative risk[a]
Sullivan, et al. (1988)	Mean age 62.8	2,188	Current use	4.4%	0.44 (0.29-0.67) for 70+ percent occlusion vs. no steriosls	0.58 (0.35-0.97)
Gruchow, et al. (1988)	Age range 50 to 75	933	Current use	15,5	0.59 (0.48-0.73) moderate vs. low occlusion score[b] 0.37 (0.29-0.46) severe vs. low occlusion score	
McFarland, et al. (1989)	Age range 35 to 59	283	Ever use	41	0.5 (0.3-0.8) for 70+ percent occlusion vs. no stenosis	**0.50**[c]
Hong (1992)	Mean age 62.3	**90**	Current use	**20**	OR for coronary artery disease = 0.13 ($p < 0.001$) in estrogen users vs. nonusers.	

KEY OR = odds ratio

[a] **95** percent confidence intervals are given in parentheses

b Value not provided.

[c] Confidence interval not provided.

Adapted from: M.J. Stampfer, and G.A. Colditz, "Estrogen Replacement Therapy and Coronary Heart Disease: A Quantitative Assessment of the Epidemiological Evidence," *Preventive Medicine 20:47-63,* 1991.

population. Among cohort studies with internal controls, seven of 12 reported reductions in heart disease risk greater than 0.5 in ERT users.

OTA's base case estimate of heart disease risk in ERT users is also consistent with all of the angiographic studies, which show 50-to 60-percent reductions in the amount of coronary artery stenosis in ERT users (table I-5). These studies of angiographically defined coronary artery disease should provide more precise estimates of heart disease risk than studies using clinical endpoints of heart attack or ischemic heart disease symptoms. This is because many postmenopausal women with significant coronary artery occlusions have no symptoms, and these women will be misclassified as having no heart disease. This misclassification diminishes the ability of an epidemiologic study of ERT users and nonusers to detect differences in risk of heart disease between the groups.

OTA's base case estimate of heart disease risk in ERT users is consistent with that of the meta-analyses by Barrett-Connor and Bush (7) (approximately 50-percent reduction in risk of heart disease in ERT users), Bush (13) (a reduction in risk of 40- to 50-percent), and Mack (60) (an estimated 50-percent reduction in risk). This is also consistent with the meta-analysis by Stampfer et al. of cohort studies with internal controls and cross-sectional angiographic studies (102). Stampfer et al. obtained a somewhat higher estimate of heart disease in ERT users when the results of cohort studies without internal controls and case control studies were also factored in to the estimate (102). OTA's estimate of relative risk of heart disease in ERT users was less than the meta-analysis of Grady et al., who calculated a relative risk of heart disease in ERT users of 0.65 (35).

Because of the uncertainty about the magnitude of the heart protective effect of ERT, OTA tested the sensitivity of the model to a wide range of estimates of heart disease risk in ERT users. Although most cohort studies have demonstrated a reduced risk of heart disease in ERT users, the range of estimates of the relative risk varies widely, to as low as 0.17. In addition, cohort studies of current ERT users have, on average, estimated a lower risk of heart disease than studies of ever users or past users of ERT. To encompass the range of estimates from these studies in our sensitivity analysis, OTA chose a relative risk of 0.2 as a best case estimate of heart disease risk in ERT users, and a relative risk of 0.8 as a worst case estimate.

OTA assumed as a base case that users of PERT would have no heart disease benefit, and as a best case, that estrogen/progestin users would have a 20-percent lower risk of heart disease than nonusers (relative risk 0.8). Randomized clinical trials examining estrogen with progestin's effect on lipids and lipoproteins suggest that the heart disease benefits of estrogen would be reduced when progestins are added, although this reduction maybe minimized by using the lowest effective dose of the least androgenic progestins.

OTA's estimates of the relative risk of heart disease in PERT users are consistent with recent epidemiologic studies. Because the addition of a progestin to ERT has become standard medical practice only relatively recently, there are few epidemiologic studies with sufficient numbers of estrogen/progestin users to estimate its impact on heart disease risk.

The evidence is weak to support a protective effect extending beyond the period of use. In the absence of such evidence, a reasonably conservative assumption is that ERT (when not combined with progestins) reduces heart disease rates by one-half, but only during the therapy period. Once HRT ceases, heart disease rates can be assumed to return quickly to the rates in the general population of women of the same age.

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Appendix J: Methods for Estimating costs

J

This appendix describes the methods and sources used in estimating cost parameters for the OTA model. The components of cost required for the model include those of bone mineral density (BMD) measurement, hormone replacement therapy (HRT), heart disease, hip fractures, gall bladder disease, endometrial cancer, and breast cancer.

The OTA model considers only those health care costs that are directly attributable to the specific conditions whose incidence or severity are affected by osteoporosis prevention strategies. They do not include any health care costs unrelated to these conditions. When an osteoporosis prevention strategy increases life spans, people are likely to use more health care simply because they are living longer. These increases in "unrelated costs" are not included in OTA's analysis, because they are assumed to be part of the portfolio of both costs and benefits embodied in the effectiveness measure (years of life gained). The basis for OTA's assumptions concerning each component is described below.

BMD SCREENING COST

The cost of screening for BMD was based on the cost of single photon absorptiometry (SPA). This is the only method of bone densitometry currently covered by Medicare (18). It is also the method used in OTA's model to estimate the distribution of BMD levels at various ages. Other BMD measurement technologies are available, generally at higher cost than SPA. The estimate of $100 used for this analysis is consistent with estimates from a variety of sources. Table J- 1 summarizes the cost estimates used in various studies of BMD screening.

HRT COST

The components of the treatment costs are summarized in table J-2. HRT regimens vary, sometimes including estrogen (ERT) alone and sometimes estrogen in combination with (or followed by) progestin (PERT).

Estrogen-Only Therapy

The annual cost of ERT, $75, was based on the retail price of Premarin™ (0.625 mg daily for 273 days per year). To arrive at this estimate OTA surveyed retail pharmacy costs in the Washington, DC area in 1991.

The American College of Obstetricians and Gynecologists recommends annual mammograms and endometrial biopsies for all women on ERT (1). However, annual mammograms are gen-

TABLE J-1: Summary of Selected Estimates of Bone Density Screening

Author/article	Data year	Cost of screening SPA	DPA	QCT	Other	Constant dollar year	Source	Comments
Health Care Financing Administration, 1993	**1990**	$1 18[a] 7 1[b]	$97[a] 6 9[b]			1990	Medicare	a Average submitted charges *b Average* allowed charges
National Osteoporosis Foundation, 1990	1990	75.50[c]	75.50[c]			1990	Estimate based on Medicare fee screens	C Average Medicare reimbursement for SPA and DPA
Vogel et al., 1991	**1990**	50-150	150-300	150-400	$ 50-$150[d] 150-300[e] 75-00[f] 50-1509	1990	Based on information obtained from hospital, clinic, and private settings	d SXA (single photon x-ray absorptiometry) e DXA (dual energy x-ray absorptiometry f Lumbar spine series g Radiogrammetry
Cummings and Black, 1986	**1984**	40-120	150-300	100-300	—	**NG**	American College of Physicians	
American Osteoporosis Alliance, 1990	1987	75	78	86	—	1987-1988	HCFA	Medicare average allowable amounts.
	1988	75	68	81	—			
Health Insurance Association of America, 1991	Claim dates: 11/1/89 to 1 0/31/90	.51[h] 116[i]	54[h] **159**	— [i] —	— —	1989-1990	Health Insurance Association of America's Medical Prevailing Healthcare Charges System	'Professional Component 'Total Component

ABBREVIATIONS: DPA = dual photon absorptiometry, NG = not given, QCT = quantitative computed tomography, SPA = single photon absorptiometry

SOURCES National Osteoporosis Foundation, *Medicare Reimbursement for Bone Mass Measurement: Costs* and savings executive summary (Washington, DC August 1990); J Petrie, U S Department of Health and Human Services, Health Care Financing Administration, personal communication, July 1993, J M Vogel, P D Ross, J W Davis, et al , Hawaii Osteoporosis Center, Honolulu, HI, "Technologies to Detect Osteoporosis" Final Report, unpublished contractor report prepared for the Office of Technology Assessment, U S Congress, Washington, DC, Mar 25, 1991 S Cummings and D Black, "Should Perimenopausal Women Be Screened for Osteoporosis?" *Annals of Internal Medicine* 104(6) 817-823, 1986, American Osteoporosis Alliance memorandum to U S House Select Committee on Aging, Subcommittee on Human Services, Washington, DC, 1990, Health Insurance Association of America, B L Harris, Associate Director, Washington, DC, letter to R C Herdman, Office of Technology Assessment, U S Congress, Washington, DC, Aug 30, 1991

erally recommended for all women over 50, so endometrial biopsy is the only cost recognized in the model. The cost of this procedure was estimated from average submitted physician charges in 40 Blue Cross/Blue Shield plans (10).

In a certain percentage of women on ERT, adenomatous or atypical endometrial hyperplasia would be detected, requiring dilatation and curettage (D&C) of the uterus. Weinstein and Schiff estimated that 7.5 percent of estrogen users would be diagnosed with endometrial hyperplasia (19). The average submitted physician charge for D&C in 40 Blue Cross/Blue Shield plans was $526 (10); therefore, the expected additional annual cost associated with this procedure for estrogen therapy users would be $39.

Most women who experience unscheduled bleeding while on estrogen replacement therapy would be given an additional endometrial biopsy. Weinstein and Schiff have estimated the incidence of bleeding in estrogen users at 2.5 percent (19). Therefore, $3 per year is added to the yearly treatment cost to account for this procedure.

On the basis of all of these estimated components of HRT cost, the total annual cost of ERT in the OTA model is $269.

TABLE J–2: Annual HRT Cost

ERT	
Prescription drug	**$ 98**[a,b]
Endometrial biopsy	129[d]
Dilation and curettage	39[e]
Additional endometrial biopsy	3[f]
Total	$269
PERT	
Estrogen	$ 98 [a,b]
Progestin	1 19[b,c]
Doctor visit	38[g]
Endometrial biopsy	3 [d, h]
Total	$258

KEY: ERT = estrogen replacement therapy; HRT = hormone replacement therapy; PERT = progestin/estrogen replacement therapy

[a]Drug cost IS from a survey conducted in 1993 by OTA of retail pharmacies in the Washington, DC area

bBased on Premarin™ (0.625 mg daily) for 273 days/year.

[c]Based on Provera™ (1 O mg daily) for 156 days/year.

dAverage submitted physician charges from 40 Blue Cross & Blue Shield plans.

e Weinstein and Schiff estimated that 7.5 percent of patients on estrogen alone would need a dilation and curettage The cost of $526 for this procedure was obtained from Blue Cross & Blue Shield average submitted physician charges.

f 2.5 percent of Patients on estrogen alone are assumed to need an additional endometrial biopsy due to increased risk of unscheduled bleeding.

g Charge is based on the 1993 Medicare average submitted charge for an established patient requiring limited service (CPT code 90050 in *Physicians' Current Procedural Terminology).*

h Unscheduled bleeding in estrogen-progestin therapy Patients would require an endometrial biopsy. The incidence of bleeding in this group is assumed to be 2,5 percent.

SOURCES: Office of Technology Assessment, 1995. R. Lapp, Manager for Provider Strategy, Blue Cross&Blue Shield Association, Chicago, IL, personal communications, July 18, 1993, and July 23, 1993. M.C, Weinstein and I. Schiff, "Cost-Effectiveness of Hormone Replacement Therapy in the Menopause," *Obstetrical and Gynecological Survey 38(8):445-455,* 1983.

Estrogen-Progestin Therapy

In PERT, a progestin is added to the estrogen regimen. The price of the progestin used in our analysis was based on Provera (10 mg daily dosage) for 12 days per four-week cycle. From a survey of retail pharmacy costs in the Washington, DC area, we estimated the annual prescription drug cost of PERT at $119.

An annual endometrial biopsy is not usually required for women on PERT, but they would have a yearly physician visit. The cost of the doctor visit, $38, was based on the Medicare charge for an established patient who receives limited service.

Most observers believe that women on PERT are not at increased risk of endometrial hyperplasia. Therefore, extra D&C procedures would not occur. PERT does result in increased frequency of abnormal vaginal bleeding, however. Ettinger and colleagues recently compared the frequency of abnormal vaginal bleeding in post-menopausal women taking cyclic PERT with a cohort of women not on HRT of any kind (8). They found a relative risk of abnormal bleeding of approximately 3.1 in women on therapy. The frequency of abnormal bleeding declined with age, however. About 60 extra events per 1,000 patient-years

TABLE J-3: Acute Myocardial Infarction Costs (1993 dollars)

Fatal acute myocardial infarction	$14,470-31 ,397a
Nonfatal acute myocardial infarction	74,217[a,b]
Ratio of nonfatal to fatal acute myocardial infarction	2.6/1 [c]
Total heart attack costs per fatal heart attack	$ 2 0[7],[4]3 [4] $[224], 3 6[1]

a E. Wittels, J Hay, and A. Gotto, "Medical Costs of Coronary Artery Disease in the United States, " *American Journal of Cardiology 65 "432-440,* 1990,

b Five_year costs discounted to their net present value at the time of the heart attack at an annual rate Of 5 perCent.

C M Stampfer, G. Colditz, W. Willett, et al , "Postmenopausal Estrogen Therapy and Cardiovascular Disease Ten-Year Follow-Up from the Nurses' Health Study, " New *England Journal of Medicine 325(11):756-762, 1991*

SOURCES" Based on data from sources cited in the footnotes

(6%) occurred in women, aged 50-54; 40 extra events per 1,000 patient-years *(470)* occurred in women aged 55-59; and about 5 extra events per 1,000 patient-years (0.5%) occurred in women aged 60-67. In an early cost-effectiveness study, Weinstein and Schiff estimated that PERT would induce abnormal bleeding in approximately 2.5 percent of patients (19). This estimate is similar to the data from the Ettinger study, if a single estimate of relative risk is used for all ages.[5] We therefore adopted 2.5 percent as an estimate of the number of cases of abnormal bleeding that would require an endometrial biopsy. Thus, $3 is added to the annual cost of HRT with progestin therapy. The total cost of estrogen/progestin treatment is therefore $258.

The components of HRT (i.e., drugs, doctor visits, tests) used in this model are similar to those used in other analyses of HRT and osteoporosis (5,15,16,19). Some analyses included only drug costs (5,15) or used drug costs plus the costs of physician visits to monitor treatment without itemizing the costs of specific diagnostic procedures included in the treatment (16). Our cost components and total cost estimates for HRT—$269 per year for ERT and $258 for PERT—are consistent with these cost estimates.

COST OF HEART DISEASE

The major cardiovascular impact of HRT is a potential reduction in the number of acute myocardial infarctions (AMIs) (i.e., heart attacks). The cost of AMI used in our analysis, shown in table J-3, reflects that of both fatal and nonfatal heart attacks.

The model assumes that there is a fixed ratio of fatal to nonfatal heart attacks. Thus, for every heart attack death assigned by the model, costs would accrue both for that woman and for a given number of additional women who would have nonfatal heart attacks.

OTA used data from the Nurses' Health Study to estimate the ratio of fatal to nonfatal heart attacks (13). That study reported the incidence of both fatal and nonfatal (confirmed and probable) AMIs in 48,470 postmenopausal nurses followed for 10 years. The observed ratio of nonfatal to fatal AMIs in that sample was 2.6.

Data from the Framingham Heart Study, a large ongoing study of heart disease incidence and outcome, gave cost estimates for fatal and nonfatal heart attacks. The study categorizes coronary artery disease into five events: acute myocardial infarction, angina pectoris, unstable angina pectoris, sudden death, and nonsudden death. Using these outcomes, Wittels and colleagues analyzed

[1] If Ettinger's estimates for the 60-67 year-old population is assumed to hold for older women as well, the average frequency across all ages would be approximately 16 per 1000 patient-years (1.6%). But as the population ages, fewer women in the cohort are alive, so this simple average underestimates the true average.

Medicare cost data, a pharmaceutical price survey, and Houston area surveys to estimate five-year costs including those for hospitalization, emergency room care, monitoring and testing, heart catheterization, and thrombolytic therapy resulting from acute myocardial infarction (20). The final cost estimates were based on these charges, weighted by their frequency of occurrence.

In the Framingham study, sudden death was defined as a change within a l-hour period from a stable clinical status to death. Nonsudden death occurs when a patient admitted with a diagnosis of AMI dies in the hospital. We used the costs of sudden and nonsudden death as the endpoints of the range of estimates for the cost of a fatal AMI. In 1993 dollars, the costs of sudden and nonsudden death from AMI were $14,470 and $31,397, respectively.

AMI patients in the Framingham Heart Study who survived hospitalization had a five-year cost (in 1993 dollars) of $81,630. This estimate was not discounted over the five-year period, and it also did not include costs incurred in years beyond the five-year period of study. To better estimate costs spread out over five years, the total was divided into five equal amounts, which were then discounted to their present value at the time of the heart attack at an annual discount rate of 5 percent. We used this discounted cost—$74,217—as the estimate of the cost of a nonfatal AMI.

Together, these estimates imply that for every heart attack death, a cost of between $207,434 and $224,361 is incurred in treating heart attacks, both fatal and nonfatal. These estimates are consistent with the few analyses that identify costs of AMI by fatal and nonfatal outcomes (9).

The costs calculated for the Framingham study included those for both men and women. If the cost of treating a female AMI patient is different from the cost of treating a male AMI patient, then the estimates used in our model may be inaccurate. Also, the expected frequencies of events or resource used in the Framingham study (based on a cohort of Massachusetts residents) may not represent the national population of coronary artery disease patients.

COST OF HIP FRACTURE

An analysis of the health care costs attributed to hip fractures is provided in a separate OTA background paper (18). The total cost includes in-hospital and post-hospital expenses as shown in table J-4. OTA used the inpatient hospital costs for patients between 50 and 64 years of age as the basis for our estimate, because it is higher than the cost for older women and therefore gives an optimistic estimate of the cost savings associated with reductions in hip fractures. The total estimated cost (including long-term care costs) is $21,189 in 1990 dollars, or $22,914 in 1993 dollars (after adjusting for inflation using the CPI-U for all items).

COST OF CHOLECYSTECTOMY

The cost of a cholecystectomy was obtained from the rates (physician and hospital costs) allowed by Blue Cross and Blue Shield of the Washington, DC region (1 1). Open cholecystectomy, which costs $11,160, was used as the basis for procedure cost estimation. Laparoscopic cholecystectomy is an increasingly frequent procedure costing approximately $9,000. This estimate is consistent with a previous analysis of gallstone treatments, which calculated the costs for a cholecystectomy - based on a 45-year-old female patient at between $6,024 and $18,072 in 1993 dollars (3).

BREAST CANCER COSTS

There are no accurate data on the lifetime cost of treating breast cancer. The existing literature provides estimates of some parts of cancer treatment, but for this analysis we constructed age- and stage-specific lifetime breast cancer cost estimates.

TABLE J-4: Average Expenditures for In-Hospital and Post-Hospital Care of Hip Fracture Patients, 1990

In-hospital care for persons age 50 to 64	
Hospital services	$ 7,732
In-hospital physician services	1,946
Anesthesia services	576
Radiologic services	298
Physical therapy	785
Total	$11,337
In-hospital for persons age 65 and over	
Hospital services	7,623
In-hospital physician services	1,236
Anesthesia services	319
Radiologic services	116
Physical therapy	28
Total	$9,322
Post-hospital for persons of all ages	
Nursing home care	7,054
Care in a rehabilitation facility or other short-stay hospital	742
Readmission to a short-stay hospital	440
Home health care	453
Nonmedical home care	329
Outpatient physician services	550
Emergency room and ambulance services	284
Total	$ 9,852
Total cost of hip fracture for patients 50 to 64	$21,189
Total cost of hip fracture for patients 65 and over	$19,174

SOURCE U.S. Congress, Office of Technology Assessment, *Hip Fracture Outcomes in People Age Fifty and Over-Background Paper,* OTA-BP-H-120 (Washington, DC U S. Government Printing Off Ice, July 1994).

The expected lifetime cost of treating breast cancer varies with the number of years of survival after detection, which is itself a function of both age and stage at detection. Age-and stage-specific l-year, 5-year, 10-year, and 15-year all-cause survival rates were provided to OTA by the National Cancer Institute from its Surveillance, Epidemiol-ogy, and End Results (SEER) tumor registry data[6] (12). These data were used to estimate the proportion of women who would live for 1 year, 3 years, 8 years, and 13 years (the midpoints of the surviv-al intervals available in the SEER data). Women who survive for at least 15 years were assumed to live 15 years plus the average life expectancy of U.S. women who reach an age equal to their age of detection plus 15 years. For example, a 65-year-old who survives 15 years to age 80 is assumed to live the average life expectancy of other 80-year-olds.

2 The SEER data on cancer incidence, stage, and survival is based on tumor registries maintained in 10 cities.

TABLE J-5: Cost of Treating Breast Cancer by Type of Care (1993 Dollars)

Treatment	Unadjusted cost	Comorbidity cost[a]	Net attributable cost
Initial care			
local	**13,500**	**1,369**	12,131
regional	14,470	1,369	13,101
distant	14,470	1,369	13,101
Continuing care	10,620/yr.	5,477/yr.	5,143/yr.
Terminal care	27,744	2,739	25,005

[a]Comorbidity cost refers to the cost of treating patients for diseases unrelated to breast cancer.

SOURCES: M. Baker, L. Kessler, N. Urban, et al., "Estimating the Treatment Costs of Breast and Lung Cancer, " *Medical Care 29(1) 40-49, 1991* U.S. Congress, Office of Technology Assessment, *Breast Cancer Screening for Medicare Beneficiaries: Effectiveness, Costs to Medicare and Medical Resources Required* (Washington, DC U.S. Government Printing Off Ice, November 1987)

For each combination of age and stage of cancer at detection, we assumed that a patient would incur an initial cost in the year of cancer onset, continuing care costs in each remaining year of life, and terminal care costs in the final year of life. Initial costs were assumed to vary with the stage of cancer at detection, whereas continuing and terminal care costs were assumed constant across allages and stages. The age- and stage-specific schedule of costs was constructed by combining these cost parameters with the age- and stage-specific survival times and discounting the costs incurred over time to their present value in the year of cancer detection at an annual rate of 5 percent.

Estimates of the cost of initial, continuing, and terminal breast cancer care are available from a study conducted by researchers at the National Cancer Institute (2). That study used data on a sample of Medicare patients to estimate the net health care costs of each kind (initial, continuing, and terminal) attributable to breast cancer.

The costs of initial care were not estimated by stage in that study, however, so OTA broke down the initial care cost into stage-specific costs using information on initial care costs by stage provided in another study (7,17). The resulting estimates of initial, continuing, and terminal care costs used in the construction of the age- and stage-specific breast cancer costs are shown in table J-5.

The resulting age- and stage-specific lifetime discounted costs are shown in table J-6.

ENDOMETRIAL CANCER COSTS

The osteoporosis prevention strategies tested in this analysis are relevant to women with intact uteri who are therefore at risk of endometrial cancer. The risk, prognosis, and treatments vary, depending on whether the woman is currently on ERT or PERT at the time of diagnosis.

OTA assumed that endometrial cancer found during HRT would have no excess associated mortality. The woman would undergo a hysterectomy and face no permanent loss of vitality. The procedure would affect costs only, not the length of life. (See appendix G for the rationale underlying this assumption.)

The cost of a hysterectomy was estimated from several published articles shown in table J-7. We used a mid-range estimate (updated to 1993 dollars) of $6,000 to include all costs (physician fees and hospitalization) associated with a hysterectomy.

If a woman is not on HRT at the time of diagnosis, the mortality risk depends on age and stage at diagnosis. The costs for this scenario were estimated in a manner similar to that used for breast cancer.

TABLE J-6: Lifetime Cost of Treating Breast Cancer,[a] by Age and Stage, in OTA's Model

Age	Stage A	Stage B	Stage C	Age	Stage A	Stage B	Stage C
50	$78,153	$67,274	$45,043	71	$50,849	$48,598	$41,285
51	76,671	66,228	44,855	72	49,250	47,527	41,173
52	75,385	65,237	44,823	73	47,340	46,161	40,893
53	73,861	63,966	44,490	74	45,605	44,911	40,679
54	73,181	63,338	44,357	75	43,951	43,818	40,619
55	71,727	62,183	44,176	76	42,293	42,685	40,375
56	70,049	61,107	43,985	77	40,825	41,824	40,352
57	69,310	60,503	43,996	78	39,127	40,514	39,778
58	67,765	59,525	43,720	79	37,542	38,638	39,071
59	66,299	58,668	43,545	80	35,414	37,169	38,497
60	65,717	58,209	43,394	81	33,403	35,869	37,960
61	64,300	57,394	43,220	82	31,637	34,781	37,433
62	63,810	57,135	43,163	83	29,572	33,515	36,655
63	62,019	56,132	42,814	84	27,703	30,667	35,044
64	60,296	55,256	42,653	85	24,941	28,835	34,364
65	59,417	54,851	42,516	86	22,334	27,156	33,643
66	57,742	53,863	42,336	87	20,056	25,791	33,089
67	57,028	53,356	42,268	88	18,209	24,528	32,533
68	54,947	52,001	41,951	89	16,673	19,099	27,503
69	53,831	51,277	41,856	**90**	12,616	15,837	26,230
70	51,885	50,091	41,601				

[a]Costs recurred in years after detection are discounted to their present value at the age of detection at a rate of 5 percent per annum

SOURCE: Office of Technology Assessment, 1995

The initial, continuing, and terminal care costs used in the estimation procedure are summarized in table J-8. We used the endometrial cancer treatment guidelines described in a cancer textbook(6) to determine the components of the cost model. The initial cost was the cost of a hysterectomy if the cancer was detected at stage I or stage 11. We used $6,000 for the cost of a hysterectomy as described above. Endometrial cancers found at more advanced stages (III or IV) are usually treated initially with intense radiation therapy. This cost was obtained from Blue Cross & Blue Shield average submitted charges for several clinical brachytherapy treatments (CPT codes 77750,77761,77762, 77776, 77777) (10). The average cost of these procedures was about $600, and assuming that the cost of radiation therapy increases with increasing dosage, we estimated that the initial treatment cost would be $1,200. The continuing cost was the annual cost of radiation therapy, $600, for no more than eight years of treatment, and the cost of annual doctor visits, $200. After consulting with an analyst at the National Cancer Institute (4), we assumed that the terminal care cost for endometrial cancer is the same as the terminal care cost of breast cancer, or $25,005.

These endometrial cancer costs were used in estimating discounted lifetime cancer costs by age and stage of onset in a cost model similar to the

TABLE J-7: Estimates of the Cost of Hysterectomy

Source	Treatment costs	Data
Summitt et al., 1992	Average hospital charge for a laparoscopy-assisted vaginal hysterectomy: $7,905 Average hospital vaginal hysterectomy charge: $2,831.05	Cost data collected from women undergoing vaginal hysterectomies at the University of Tennessee, Memphis Gynecological Clinic.
Kovac et al., 1991	Average hospital abdominal hysterectomy charge: $3,584.82 Average hospital vaginal hysterectomy charge: $2,831.05	Based on data collected from all patients undergoing hysterectomies in a St. Louis Missouri hospital between January 1, 1986 and December 31, 1986.
Health Care Financing Administration, 1991	Average physician charge for an abdominal hysterectomy: $2,020 (submitted) $890 (allowed)	Medicare Part B data, Office of Research and Demonstrations
Blue Cross & Blue Shield, 1990 (Lapp, 1 993)	Average submitted charges for physician services for a total abdominal hysterectomy: $1,906	Based on data gathered from 40 Blue Cross plans (New York and California not included.)
Tosteson et al., 1990	Abdominal hysterectomy: $4,900 (based on stage 1, charge includes hospital care and professional fees)	Physician fees based on Medicare prevailing charges or charges at selected Boston-area teaching hospitals

SOURCES: R.L. Summitt, Jr., T.G. Stovell, G.H. Lipscomb, et al., "Randomized Comparison of Laparoscopy-Assisted Vaginal Hysterectomy with Standard Vaginal Hysterectomy in an Outpatient Setting," Obstetrics and Gynecology 80(6):895-901, 1992, S R Kovac, S.J. Christie and G.A. Bindbeutel, "Abdominal Versus Vaginal Hysterectomy' A Statistical Model for Determining Physician Decision Making and Patient Outcome, " *Medical Decision Making* 11(1):19-28, *1991,* J. Petrie, U S Department of Health and Human Services, Health Care Financing Administration, personal communication, July 1993; R. Lapp, Manager for Provider Strategy, Blue Cross&Blue Shield Association, Center for Health Economics and Policy Research, Chicago, IL, personal communications, July 18, 1993, and July 23, 1993; A.N.A. Tosteson, D.I. Rosenthal, J Melton, Ill, et al., "Cost Effectiveness of Screening Perimenopausal White Women for Osteoporosis: Bone Densitometry and Hormone Replacement Therapy, " *Anna/s of Internal Medicine* 113(8):594-603, 1990.

TABLE J-8: Endometrial Cancer Costs (1993 Dollars)

Initial care:	
All stages (hysterectomy)	$6,000
Stages Ill and IV (radiation treatment)	1,200
Continuing care:	
Annual doctor visits	**200**
Annual radiation therapy	**600**
Terminal care	**25,005**

SOURCE: Office of Technology Assessment, 1995

one for breast cancer. The lifetime costs due to endometrial cancer were discounted by 5 percent per year to the age of onset and weighted by the probability of surviving for different lengths of time, based on age- and stage-specific all-cause survival rates provided to OTA by the National Cancer Institute (12). These costs are shown in table J-9 (see page 210).

TABLE J-9: Lifetime Cost of Treating Endometrial Cancer,[a] by Age and Stage, in OTA's Model

Age	Stage A	Stage B	Stage C	Age	Stage A	Stage B	Stage C
50	$15,702	$20,203	$21,552	71	$15,178	$21,482	$22,964
51	15,796	20,467	21,679	72	15,297	21,677	23,064
52	15,925	20,635	21,804	73	15,418	21,891	23,166
53	16,018	20,888	21,964	74	15,599	21,993	23,220
54	16,053	20,985	22,027	75	15,780	21,177	23,322
55	16,207	21,241	22,227	76	15,837	22,119	23,151
56	16,286	21,370	22,317	77	15,941	22,136	23,005
57	16,317	21,509	22,376	78	16,048	22,167	22,863
58	16,394	21,681	22,521	79	14,949	21,015	21,970
59	16,491	21,862	22,623	80	15,114	21,178	21,927
60	16,519	21,932	22,713	81	15,254	21,291	21,882
61	16,581	22,138	22,810	82	15,401	21,474	21,848
62	16,610	22,154	22,860	83	15,742	21,588	21,806
63	16,670	22,351	22,988	84	13,643	19,375	21,028
64	16,733	22,473	23,055	85	13,605	19,438	20,993
65	16,781	22,549	23,165	86	13,525	19,443	20,935
66	16,807	22,660	23,158	87	13,505	19,509	20,892
67	16,831	22,726	23,177	88	13,517	19,648	20,880
68	16,898	22,851	23,224	89	8,990	13,546	15,996
69	16,920	22,907	23,238	90	8,635	13,418	15,890
70	17,014	23,021	23,292				

[a]Costs incurred in years after detection are discounted to their present value at the age of detection at a rate of 5 percent per annum

SOURCE: Office of Technology Assessment, 1995

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Appendix K: Abbreviations and Glossary

K

1,25 OH_2D_3	calcitriol or 1,25 dihydroxyvitamin D_3
ACOG	American College of Obstetricians and Gynecologists
AHCPR	Agency for Health Care Policy and Research (DHHS)
AMI	acute myocardial infarction
BMC	bone mineral content
BMD	bone mineral density
CEA	cost-effectiveness analysis
CHD	coronary heart disease
CVA	cerebrovascular accident
CVD	cardiovascular disease
DES	diethylstilbestrol
DEXA	dual energy x-ray absorptiometry
DHHS	U.S. Department of Health and Human Services
DPA	dual photon absorptiometry
ERT	estrogen replacement therapy
FDA	Food and Drug Administration (DHHS)
HCFA	Health Care Financing Administration (DHHS)
HDL	high-density lipoprotein cholesterol
HRT	hormone replacement therapy
IHD	ischemic heart disease
IU	international units
IV	intravenous
LDL	low-density lipoprotein cholesterol
MI	myocardial infarction
MPA	medroxyprogesterone acetate
MRI	magnetic resonance imaging
NCI	National Cancer Institute (NIH)
NHLBI	National Heart, Lung, and Blood Institute (NIH)
NIA	National Institute on Aging (NIH)
NIAMS	National Institute of Arthritis, Musculoskeletal and Skin Diseases (NIH)
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases (NIH)
NIH	National Institutes of Health (DHHS)
NOF	National Osteoporosis Foundation
OB-GYN	obstetrics and gynecology
OHTA	Office of Health Technology Assessment (AHCPR)
OTA	Office of Technology Assessment
PEPI	Postmenopausal Estrogen/ Progestin Interventions Trial
PERT	combined estrogen/progestin replacement therapy
PHS	Public Health Service
QALY	quality-adjusted life year

QCT	quantitative computed tomography
SC	subcutaneous
SPA	single photon absorptiometry
SXA	single photon x-ray absorptiometry
USP DI	U.S. Pharmacopoeia Dispensing Information
VLDL	very low-density lipoprotein cholesterol

19-nortestosterone
A form of progestin.

Amenorrhea
The absence or abnormal cessation of menstruation.

Anabolic steroid
Any of a group of synthetic derivatives of the androgen testosterone (a sex steroid or hormone) having pronounced anabolic properties and relatively weak androgenic properties. Anabolic steroids such as dromostanolone, ethylestrenol, nandrolone, oxandrolone, oxymetholone, and stanozolol are used clinically mainly to promote growth and repair of body tissues in senility, debilitating illness, and convalescence.

Androgen (or androgenic hormone)
Naturally occurring male sex hormones (e.g., testosterone, androsterone, and dehydroepiandrosterone) and substances that exert biological effects characteristic of these hormones (e.g., the synthetic compound methyltestosterone). Androgens inhibit bone resorption and increase calcium absorption in the intestine, but also have serious side effects.

Androgenic
Any substance, e.g., androsterone and testosterone, that stimulates male characteristics.

Angina
Any spasmodic, choking, or suffocating pain. The term is often used to denote angina pectoris—a condition characterized by severe, transient chest pain, accompanied by a feeling of suffocation, is due to a deficiency in blood supply to the heart.

Angiography
See *arteriography*.

Anovulation
The absence of ovulation (development and release of an ovum from the ovary).

Appendicular skeleton
The bones of the extremities, including all of the bones of the limb girdles.

Arteriography
A diagnostic procedure that allows blood vessels to be seen on X-ray film after the injection of contrast material into the bloodstream; used to detect abnormalities such as obstructions, aneurysms, clots, tumors, and injured organs.

Arteriosclerosis
A general term that describes thickened and hardened arteries, the condition that leads to most cases of heart disease and a significant proportion of cerebrovascular disease in the United States.

Atherogenesis
The formulation of patchy plaques of fatty or lipid material on the inner lining of the arteries, restricting blood flow and encouraging the development of blood clots; can result in sudden stoppage of blood flow to the heart.

Atherosclerosis
A descriptive term for thickened and hardened lipid-rich lesions of the medium and large muscular arteries; classified into two forms: early lesions, consisting of fatty streaks, and advanced lesions, consisting of fibrous plaques; commonly occurs in arteriosclerosis, in which deposits of fibrous and cellular tissue, cholesterol, and fat accumulate in large and medium-sized arteries, impeding blood flow; responsible for the majority of cases of myocardial and cerebral infarction.

Axial skeleton
The spine, ribs, sternum, and skull.

Bilateral oophorectomy
Surgical removal of both ovaries.

Bioavailability
The degree to which a drug or other substance becomes available to the target tissue after administration.

Bioequivalence
The requirement that a generic product include the same therapeutic ingredient, and that its rate and extent of absorption be the same as the innovative product.

Bisphosphonates
Chemical compounds developed during the past 20 years for treatment of various bone diseases. Basically, they are carbon-substituted analogues of pyrophosphate (an endogenous physiologic inhibitor of bone mineralization).

Several bisphosphonates are under investigation as therapeutic agents for osteoporosis, among them **etidronate, clodronate, tiludronate, pamidronate, risedronate, and alendronate.** Bisphosphonates are considered experimental (investigational) in the prevention and treatment of osteoporosis in the United States.

Blinding
A technique used in a randomized clinical trial (RCT) to prevent bias by preventing the patients and/or investigators involved in the trial from knowing which participants are receiving which treatment. In a **single-blind RCT,** the patients in the trial are "blind" as to which individuals in the study are receiving the experimental or control treatment. In a **double-blind RCT,** both the investigators and the patients are "blind" as to which individuals in the study are receiving the experimental treatment and which are receiving control treatment. Additional layers of blinding can be added, as, for example, when a third individual (usually the evaluator of outcomes, the individual analyzing the data) also is unaware of treatment assignments.

Body mass index (BMI)
Weight in kilograms divided by height in meters squared. A measure used to define normal ranges of body weight.

Bone
A specialized connective tissue in which a matrix consisting of collagen fibers, a large variety of other proteins and ground substances is impregnated with a solid mineral. Bone is the dynamic and complex tissue of which the bones in the adult skeleton of humans and other vertebrates is largely composed. The skeleton is composed of two kinds of bone: an outer, dense shell of **cortical** (or **compact** or **haversian) bone** and an inner, open, sponge-like region of **cancellous** (or **trabecular) bone.** About 80 percent of the mass of the skeleton is cortical bone, and 20 percent is cancellous bone.

Bone densitometry
A term used to refer to a range of noninvasive techniques that use a densitometer to measure the density of bone (e.g., SPA, DEXA, DPA, SXA) and is used to detect osteoporosis.

Bone density
The mass of bone substance per unit volume (g/cm^3).

Bone mineral content (BMC)
The mass of bone divided by the one dimensional length of bone measured expressed as grams per cm.

Bone mineral density (BMD)
The mass of bone divided by the two dimensional projected area of the bone measured, expressed as mass per unit area (g/cm^2).

Calcaneus
The heel bone.

Calcitonin, human
One of the three calcium-regulating hormones in humans, the others being human parathyroid hormone (hPTH) and calcitriol.

Calcitriol (1,25 OH_2D_3, 1,25-dihydroxyvitamin D_3 or 1,25-dihydroxycholecalciferol)
One of several vitamin D metabolizes.

Calcium
The most abundant mineral element in the human body. In humans, calcium is an essential nutrient not only for the normal mineralization of bones

and teeth but also for regulating intracellular events in most, if not all body tissues.

Cancellous (or trabecular) bone

The inner, open, sponge-like region of bone prevalent in the vertebrae and in the pelvis, the main sites of osteoporotic fractures. About 20 percent of the mass of the skeleton is cancellous bone. Compare *cortical bone.*

Carcinogen

An agent that causes cancer (e.g., certain chemicals, ionizing radiation, tobacco smoke, asbestos fibers, and estrogen).

Carcinoma

A cancer arising from epithelial cells, including the external epitheliums (mainly skin and linings of the gastrointestinal tract, lungs, and cervix) and the internal epitheliums that lines various glands (e.g., breast, pancreas, uterus, and thyroid).

Cardiac arrhythmias

Variations from the normal rate or rhythm of heart beats.

Cardiac catheterization

Passage of a small catheter through a vein or artery into the heart for the purpose of securing blood samples, determining intracardiac pressures, and detecting cardiac anomalies.

Cardiovascular disease (CVD)

Any of a diverse group of diseases affecting the heart, blood vessels, and/or blood circulation. CVD includes diseases of the heart muscle itself, ischemic heart disease, hypertension, cerebrovascular diseases, and various other conditions.

Case-control study

A type of observational study, where the frequency of a suspected causative factor, such as estrogen use, is compared in a group of people who have a disease (cases) and those who do not (controls). If this factor is found with greater frequency in those with disease, a causal association may be suspected. Results of the comparison may be expressed as the relative risk. See *relative risk.*

Cerebral infarction

An area of dead tissue in the cerebrum caused by an interruption of blood circulation due to functional constriction or actual obstruction of a blood vessel, hemorrhage, etc. Also known as a stroke or cerebrovascular accident (CVA).

Cerebrovascular disease

Any disease of the blood vessels supplying blood to the brain or of the brain's covering membranes (meninges), characterized by rupture of the blood vessels or inadequacy of blood to the brain. Common causes include atheroma, hypertension, cerebral thrombosis, or embolism.

Cholecystectomy

Surgical removal of the gall bladder.

Cholesterol

A sterol present in animal tissues (e.g., cell membranes, blood plasma, and lipoproteins), involved in physiological processes, such as the manufacture of bile acids, sex hormones, and adrenocorticoid hormones; also involved in the development of pathological processes such as atherosclerosis. See also *high-density lipoprotein cholesterol* and *low-density lipoprotein cholesterol.*

Climacteric

The syndrome of endocrine, somatic, and psychic changes occurring at the end of the female reproductive period (menopause).

Clinical trial (also called therapeutic trial)

A research activity that involves the administration of an experimental prophylactic, diagnostic, or therapeutic agent, device, regimen, procedure, etc. to humans to evaluate its safety and effectiveness. The term is subject to wide variation in usage, from the first use in humans without any control treatment to a rigorously designed and executed experiment involving test and control treatments and randomization. See also *randomized clinical trial (RCT).*

Coagulation

The process of certain particles joining together to form larger masses.

Coagulation proteins
Proteins found in the plasma that aid in the coagulation process of blood (e.g., Factor VIII, Factor IX. antihemophilic factor, or prothrombin). Also called "clotting factors."

Cohort study
A type of observational study, where the investigator begins with a group of subjects (the "cohort"), some or all of whom are exposed to a suspected causative factor, and follows this cohort over time for development of a disease. Comparison is made with a control group composed of unexposed members of the cohort **(internal controls),** or to subjects outside the cohort who are similar to members of the cohort, but who have not been exposed to the suspect factor **(population, community, or external controls).**

Cones fracture
Fracture of the wrist.

Compact bone
See *cortical bone*

Comparison group
In a cohort study, the group of unexposed members to which the exposed members are compared. In case-control studies, the group of subjects without disease to which the subjects with disease (the cases) are compared.

Confidence interval
Conventionally, a 95-percent confidence interval is used, which implies that there is a 95-percent chance that the true relative risk being measured falls within the interval, and a 5-percent risk that it does not.

Confounding variables
Variables related to both the disease and the exposure under study that can explain or alter all or part of an observed association.

Conjugated estrogens
An amorphous preparation of naturally occurring, water-soluble, conjugated forms of mixed estrogens, chiefly sodium estrone sulfate, extracted from the urine of pregnant mares; suitable for parenteral, oral, and topical administration and used in estrogen hormone therapy. The conjugated estrogens have pharmacologic effects similar to those of endogenous estrogens.

Consensus conference
A meeting of scientists, medical practitioners, and informed lay people to review scientific information about biomedical technologies and to develop a consensus statement on the clinical application of current medical findings.

Coronary artery bypass graft (CABG) surgery
A surgical procedure in which a vein or an artery is used to bypass a constricted portion of one or more coronary arteries. This procedure has become the primary surgical approach to the treatment of coronary artery disease.

Coronary artery disease (CAD)
Narrowing or blockage of the coronary arteries, which usually results in reduced blood flow to the heart muscle.

Coronary perfusion
The pumping of a fluid through the heart by way of an artery.

Cortical (or compact or haversian) bone
The dense outer shell of bone. One of the two general structural categories of the bone tissue making up the skeleton, cortical bone consists of tightly packed layers of bone. It forms the outer shell of all bones and is prevalent in the shafts of the long bones of the arms and legs. About 80 percent of the mass of the skeleton is cortical bone. Compare *cancellous bone.*

Cost-effectiveness analysis (CEA)
An analytical technique that compares the costs of a project or of alternative projects to the resultant benefits, with costs and benefits/effectiveness expressed by different measures. Costs are usually expressed in dollars, but benefits/effectiveness are ordinarily expressed in terms such as "lives saved," "disability avoided," "quality-adjusted life-years saved," or any other relevant objectives.

Cross-sectional study
In epidemiology, an observational study that examines the relationship between diseases (or other health-related characteristics) and other variables

of interest as they exist in a defined population at one particular time. The temporal sequence of cause and effect cannot necessarily be determined in a cross-sectional study.

Cyclic regimen
Interrupted episodes with ongoing medication. In cyclic regimens of estrogen and progestin, estrogen is usually given for 21 days each month, and a progestin is given with estrogen for the last 7 to 14 days of those 21 days.

Densitometry
See bone densitometry

Diethylstilbestrol (DES)
A synthetic estrogenic compound used to treat menopausal symptoms, vaginitis, and suppressed lactation.

Discounting
A procedure used in economic analysis to express as "present values" those costs and benefits that will occur in future years. Discounting is based on two premises: 1) individuals prefer to receive benefits today rather than in the future; and 2) resources invested today in alternative programs could earn a return over time.

Double blind
See *randomized clinical trial (R CT)* and *blinding.*

Dual energy x-ray absorptiometry (DEXA)
A bone densitometry technique similar to DPA but uses an x-ray machine rather than a radioactive material to produce a dual-energy radiation beam. Different manufacturers use different terms for this technology (e.g., quantitative digital radiography (QDR), dual-energy radiography (DER), dual energy radiographic absorptiometry (DRA), and dual x-ray absorptiometry (DXA).

Dual photon absorptiometry (DPA)
A bone densitometry technique that uses a dual-energy radioactive material (usually gadolinium- 153) as the source of a dual-energy radiation beam; the dual-energy beam allows measurement of bone and soft tissue without the necessity of encasement in water required in SPA or SXA. The site of measurement for DPA is typically the hip or spine. DPA is sometimes used to measure bone mass in the whole body and can be used to measure bone mass in the forearm, distal radius (wrist), and calcaneus (heel).

Duration of exposure
The length of time a person or test animal is exposed to a chemical.

Dysmenorrhea
Difficult and painful menstruation.

Dyspareunia
Difficult or painful coitus/intercourse in women.

Dysuria
Painful or difficult urination.

Effectiveness
The same as efficacy (see below) except that it refers to ". . . average or actual conditions of use."

Efficacy
The probability of benefit to individuals in a defined population from a medical technology applied for a given medical problem under ideal conditions of use. Efficacy is generally evaluated in controlled trials of an experimental therapy and a control condition. Compare to *effectiveness.*

Endogenous
Produced within or caused by factors within the organism.

Endometrial biopsy
The microscopic examination of a sample of cells, obtained from the lining of the uterus, in order to evaluate ovulatory function and/or to detect the presence of hyperplasia, dysplasia, or cancer.

Endometrium
The tissue lining the inner uterus, the thickness and structure of which vary with the phase of the menstrual cycle.

Endothelium
The layer of epithelial cells that lines the cavities of the heart and of the blood and lymph vessels, and the serious cavities of the body.

Epidemiological studies
Studies concerned with the relationships of various factors determining the frequency and dis-

tribution of specific diseases in a human community.

Epidemiology
The scientific study of the distribution and occurrence of human diseases and health conditions, and their determinants.

Equine estrogen
Estrogen pertaining to, characteristic of, or derived from the horse. See *conjugated estrogens.*

Erythema
Redness of skin due to congestion of the capillaries.

Esterified estrogen
A mixture of the sodium salts of sulfate esters of estrogenic substances; used for oral estrogen therapy.

Estradiol
The most potent naturally occurring estrogen in humans.

Estrogen
A generic term for estrus-producing compounds; the naturally occurring female sex hormones, including **estradiol, estriol,** and **estrone.** The term also refers to substances occurring in plants or made synthetically (as **benzestrol** or **diethylstilbestrol)** that have biologic activity similar to that of estrogens produced in the ovaries of female mammals.

Estrogen replacement therapy (ERT)
The use of estrogen for the relief of menopausal symptoms, e.g., hot flashes, the prevention of heart disease, and the prevention of osteoporosis.

Estrone
An estrogen isolated from pregnancy urine, the human placenta, and palm kernel oil, and also prepared synthetically.

Etidronate
A bisphosphonate ($C_2H_6NA_20_7P_2$) that was patented as a therapeutic agent for calcium disorders in 1972 by Procter& Gamble, parent company of Norwich Eaton Pharmaceuticals, Inc. Oral etidronate is indicated for the treatment of Paget's disease and some other conditions, but it has not been approved by FDA for osteoporosis. As of 1995, etidronate was the only bisphosphonate available on the U.S. market. Neither etidronate nor any other bisphosphonates have been approved by FDA for indications related to osteoporosis.

Etiology
The cause or origin of disease.

Exogenous estrogen
Estrogen that is not produced within the body but is provided by other means, e.g., tablets, injection, cream.

External controls
In a cohort study, individuals not part of the cohort and who have not been exposed, with which the exposed members of the cohort are compared. In a clinical trial, individuals not formally enrolled in the trial who have had an alternative treatment, with which the experimentally treated group is compared. External controls may be historical or concurrent.

External validity
A measure of the extent to which study results can be generalized to the population that is represented by individuals in the study, assuming that the characteristics of that population are accurately specified.

Femur
The thigh bone, the bone that extends from the hip to the knee. It is the longest and largest bone in the body.

Fibrin
A white insoluble protein formed at the site of an injury from fibrinogen that becomes the foundation of a blood clot.

Fibrinogen
A soluble plasma protein synthesized in the liver, which is involved in blood coagulation as the precursor of fibrin. Also called "Factor I."

Fibroblast
A connective tissue cell, found in the skin.

First-pass hepatic effect
See hepatic effect.

Functional impairment
A deficit in an individual's ability to function independently. Functional impairments in elderly people are often described in terms of deficits in activities of daily living (ADLs) and instrumental activities of daily living (IADLs).

Grade
The histological appearance of a cancer cell. In oncology, the classification of cancer according to the degree of differentiation of the cancer cell. More differentiated cell types are generally less malignant.

Haversian bone
See *cortical bone.*

Healthy user effect
A phenomenon in epidemiologic studies in which subject participants exhibit lower incidence of morbidity or mortality than the general population because they are generally in good health while the less healthy either choose not to participate in the study or are excluded.

Hemostatic
The arrest of bleeding, whether by the physiological properties of vasoconstriction and coagulation or by surgical means.

Hepatic effect
Pertaining to the liver, the metabolism of estrogen by the liver.

Hepatobiliary
Related to the gallbladder.

High-density lipoprotein cholesterol (HDL)
A class of cholesterol; low levels of HDL are associated with an increased risk of heart attack.

Histology
Microscopic anatomy. The study of the minute anatomical structure, composition, and function of the tissues.

Historical controls
In nonrandomized clinical trials, individuals treated with a "control treatment" outside the study proper, at some time previous to the trial, against which the experimentally treated individuals are compared. In a cohort study, unexposed individuals outside of the cohort, at some time previous to the cohort observation period, against which the exposed members of the cohort are compared.

Hormone
A specific organic product of living cells that, transported by body fluids, produces a specific effect on the activity of cells remote from its point of origin (e.g., metabolism, growth, and the development of secondary sex characteristics, such as breasts and facial hair). Examples of such hormones include insulin, estrogen, progestin, testosterone, adrenaline, and thyroxine. Also a synthetic substance that resembles a naturally occurring hormone in producing a specific biological effect.

Hormone replacement therapy (HRT)
This term describes either estrogen replacement therapy or combined estrogen and progestin replacement therapy when a distinction is not necessary.

Hospital-based case-control studies
In this type of study, all cases diagnosed with the disease under study in one or more hospitals are compared with patients in the same hospitals who do not have the disease.

Hot flash
Sudden sensations of heat and flushing of the face and torso, associated with menopause.

Hypermenorrhea
Excessive menstrual bleeding, but occurring at regular intervals and being of usual duration.

Hyperplasia
Abnormal increase in the number of normal cells in normal arrangement in an organ or tissue, which increases its volume.

Hypertension
Elevated pressure, usually referring to high blood pressure—a common and significant cardiovascular disorder characterized by persistently high arterial blood pressure, usually greater that 140mm Hg systolic and 90mm Hg diastolic pressure.

Hypertriglyceridemia
An excess of triglycerides in the blood.

Hysterectomy
Surgical removal of the uterus, in some cases also including the cervix, ovaries, oviducts, and pelvic lymph nodes.

In vitro
Literally "in glass"; pertaining to a biological process or reaction taking place in an artificial environment, usually a laboratory.

In vivo
Literally "in the living"; pertaining to a biological process or reaction taking place in a living cell or organism.

Incidence
In epidemiology, the number of new cases of disease, infection, or some other event having their onset during a prescribed period of time in relation to the unit of population in which they occur. The **incidence rate is** the number of new cases of specified disease divided by the number of people in a population over a specified period of time, usually 1 year.

Infarction
Necrosis (death) of tissue, resulting from the interruption of blood supply (e.g., as in a heart attack (myocardial infarction)).

Internal controls
A control group composed of unexposed members of a cohort. See *cohort study*.

Internal validity
A measure of the extent to which study results reflect the true relationship of a "risk factor" (e.g., treatment or technology) to the outcome of interest in study subjects.

Ischemia
Insufficient blood supply to meet the full physiologic needs of the tissue for oxygen (but short of the degree of ischemia that results in necrosis), usually due to atherosclerosis, but also due to injury to blood vessels, muscle spasm, or inefficient pumping of the heart.

Ischemic heart disease (IHD)
A spectrum of conditions caused by insufficient oxygen supply to the heart muscle, and the leading cause of death in the United states. The most common manifestations of IHD are angina. acute myocardial infarction (heart attack), and sudden death.

Latency
Time since first exposure to a suspected causative factor.

Latent effect
A reaction to a substance that is not immediately evident but that appears later in life; also referred to as a silent effect.

Life expectancy
An expected number of years of life based on statistical probability.

Lipids
A group of organic compounds, classified into complex lipids (e.g., fatty acids, phospholipids, cholesterol) and simple lipids (e.g., steroids). Lipids are central to a wide variety of metabolic and structural functions in the body, such as energy storage, formation of hormones and bile acids, and structure of cell membranes.

Lipoprotein
Compounds consisting of lipids (fatty substances such as cholesterol) and proteins, the form in which lipids are transported in the blood and lymph fluid. Lipoproteins form the main structural components of cell membranes and cell organelles. They are classified as very low-density (VLDL), low-density (LDL), and high-density (HDL) lipoprotein cholesterol.

Low-density lipoprotein cholesterol (LDL)
A class of cholesterol; high levels of LDL are associated with a greater risk of heart attack.

Magnetic resonance imaging (MRI)
A diagnostic technique that produces cross-sectional images of organs and structures in the body by measuring the reaction of nuclei (typically of hydrogen protons) in magnetic fields to radio fre-

quency waves. MRI has also been used to measure bone density.

Matching
A method of minimizing the impact of confounding factors. Controls may be matched to cases to try to minimize other differences between groups. Matching may be done with groups of subjects (stratification) or with individuals, and may be done with highly specific characteristics, such as age, age at menopause, family history of the disease, etc.

Medicare
A nationwide, Federally administered health insurance program authorized by Title XVIII of the Social Security Act in 1965 to cover the cost of hospitalization, medical care, and some related services for eligible persons over age 65, persons receiving Social Security Disability Insurance payments for 2 years, and persons with end-stage renal disease. Medicare consists of two separate but coordinated programs—hospital insurance (Part A) and supplementary medical insurance (Part B). Health insurance protection is available to insured persons without regard to income.

MEDLINE database
The original, largest, and most utilized database in the National Library of Medicine's computerized retrieval and technical processing system. MEDLINE contains references to biomedical and other literature relevant to health and health services.

Medroxyprogesterone acetate (MPA)
A form of progestin. Also known as Provera (Wyeth-Ayerst). In the United States, MPA is the most commonly used progestin in combined estrogen/progestin replacement therapy.

Membership bias
Bias introduced when the group or cohort being studied is unrepresentative of the population at large, so that comparisons and extrapolations to the population group are unjustified.

Menarche
The onset of menses at puberty.

Menopausal syndrome
Symptoms associated with menopause, e.g., hot flashes, vaginal dryness, osteoporosis.

Menopause
Cessation of menstruation; the immediate postreproductive phase of a woman's life, when menstrual function ceases due to failure to form ovarian follicles and ova. Menopause occurs naturally around the age of 50. Menopause is also a secondary consequence of surgical removal of the ovaries, and of certain illnesses (e.g., premature ovarian failure).

Menorrhagia
Excessive menstruation.

Menses
The monthly flow of blood from the female genital tract.

Meta-analysis
A statistical process used to pool results from a number of studies (e.g., from many small randomized clinical trials) to enable the demonstration of statistically significant differences when the results are combined.

Metastasis
The process by which malignant cells spread to distant body sites via the lymphatic circulation of the bloodstream; also, a secondary malignant tumor.

Metrorrhagia
Uterine bleeding, usually of normal amount, occurring at completely irregular intervals, the period of flow sometimes being prolonged.

Morbidity
The condition of being ill or otherwise afflicted with an unhealthful condition.

Morbidity rate
The rate of illness in a population, calculated as the number of people ill during a time period divided by the number of people in the total population; used to refer to incidence or prevalence rates of disease.

Mortality rate
The death rate, often made explicit for a particular characteristic; e.g., age, sex, or specific cause of

death. A mortality rate contains three essential elements: 1) the number of people in a population group exposed to the risk of death (the denominator); 2) a time factor; and 3) the number of deaths occurring in the exposed population during a certain time period (the numerator).

Myocardial infarction (MI)
Heart attack. Sudden necrosis (death) of tissue in the myocardium (heart muscle) characterized by severe, unremitting chest pain. leading to arrhythmias and/or heart failure; in most cases, caused by coronary atherosclerosis (obstruction of coronary vessels, leading to insufficient blood supply to the heart muscle).

Myocardium
Muscle of the heart.

Natural estrogen
An estrogen derived from natural sources, (i.e., not synthetic), such as conjugated equine estrogens, estradiol, or estriol.

Natural menopause
Menopause that occurs as a natural part of the aging process; not surgically induced.

Naturally occurring estrogenic hormones
Female sex hormones produced by the ovaries, the placenta, testes, and possibly the adrenal cortex.

Neoplasm
Uncontrolled and progressive growth of tissue, either benign or malignant; a tumor.

Nested case-control studies
Case-control studies conducted, or "nested," within a cohort group.

Nonischemic heart disease
Heart disease from causes other than coronary artery disease (e.g., congenital heart disease, myocardiopathy).

Norethidrone acetate
.4 progestational agent similar in action to progesterone.

Observational study
An epidemiologic study in which the experiences of the groups being compared are simply observed (e.g., case-control studies, cross-sectional studies, and cohort studies). Such studies are the traditional source of information on suggestive associations in epidemiology.

Occlusion
In the context of the vascular system, the blocking off or obstruction of blood flow through a vessel.

Odds ratio
A measure of association closely related to relative risk; the ratio of the odds of a disease occurring in individuals exposed to the risk compared to those unexposed. For large samples, the odds ratio is essentially equal to the relative risk.

Oligomenorrhea
Abnormally infrequent menstruation.

Oophorectomy
Excision of one or both ovaries.

Opposed estrogen
Estrogen used in conjunction with progestin.

Osteoblast
A cell arising from a fibroblast, which, as it matures, is associated with bone production.

Osteopenia
A reduction in the amount of bone mass, leading to fractures after only minimal trauma.

Osteoporosis
A systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture.

P value
In epidemiologic studies, the probability of concluding that a statistical association exists between, for instance, a risk factor and a health endpoint, when, in fact, there is no real association; the likelihood that an observed association in a study is due to the play of chance. Also called "Type I error" or "alpha," and commonly called the level of significance. See *significance level.*

Parathyroid hormone (PTH) or human parathyroid hormone (hPTH)
A polypeptide hormone which regulates the concentration of extracellular fluid calcium.

Parenteral
Administration through routes other than the alimentary canal. Parenteral administration includes intravenous. subcutaneous, transdermal, intraocular, and intranasal administration.

Pathophysiology
The physiology of disordered function.

Percutaneous
Literally, "through the skin"; refers to a surgical procedure that requires only a very small incision, such as a biopsy, or aspiration of fluid beneath the skin using a needle, catheter, or syringe.

Perimenopause
The time around the menopause.

Peripheral conversion
Conversion of estrogen outside of the liver, in peripheral tissues.

Peripheral nervous system
The autonomic nervous system, the cranial nerves, and the spinal nerves including associated receptors.

Pharmacodynamics
The study of the actions of drugs on living systems.

Pharmacokinetics
The rate of change in a physical or chemical system, specifically in relation to drugs.

Placebo
A drug or procedure with no intrinsic therapeutic value. In a **placebo-controlled** randomized clinical trial, a placebo is given to patients in control groups as a means to blind investigators and patients as to whether an individual is receiving the experimental or control treatment. See *randomized clinical trial (RCT).*

Plaques
Yellowish fatty deposits formed within the intima and inner media (innermost and middle coats of the blood vessels) of large and medium-sized veins.

Platelets
Disk-shaped tissue, found in the blood of mammals, which responds to injury elsewhere in the body. Platelets are known for their role in blood coagulation (clotting). Also called "thrombocytes."

Population-based case-control studies
In this type of study, all cases diagnosed in the community or in a sample of the general population are compared with controls selected from the community or a sample of the general population.

Postmenopause
The period of time after the menopause.

Power
The power of the study refers to the chance of finding a true difference in risk and labeling it as statistically significant. Thus the power of the study is equal to 0.80 when the sensitivity level is 0.20 (i.e., 1- 0.20= 0.80).

Predictive test
A medical test generally applied to asymptomatic individuals to provide information regarding the future occurrence of disease.

Premarin
Wyeth-Ayerst's brand of conjugated estrogen. The most commonly used estrogen for HRT in the United States. See *conjugated estrogens.*

Premature ovarian failure
Condition characterized by the failure to ovulate before the normal age of menopause.

Premenopause
The stage of life before menstruation stops.

Premenstrual syndrome
The pattern of symptoms related to the menstrual cycle.

Preovulation
The first 14 days of a woman's menstrual cycle, when estrogen levels are rising before ovulation takes place.

Prevalence
A measure of the number of individuals in a given population who have a specific disease or other condition at a designated time (or during a particular period).

Primary prevention
A category of health and/or related interventions that aim to eliminate a disease or disordered state before it can occur. Compare *secondary prevention.*

Progestational
Favoring pregnancy; conducive to gestation; having a stimulating effect upon the uterine changes essential for the implantation and growth of the fertilized ovum. Referring to *progesterone,* or to a drug with progesterone-like properties.

Progesterone (also called progestational hormone)
An antiestrogenic female sex hormone secreted by the ovaries (specifically by the corpus lutetium, formed immediately after ovulation), by the placenta during pregnancy to prepare the inner lining of the uterus for implantation of an ovum, and in small amounts by the adrenal glands and testes, and prepares the inner lining of the uterus for pregnancy. Receptors for progesterone have been identified on osteoblasts, and although the data are not entirely clear, it appears that progesterone may stimulate bone formation. Progesterone and other agents capable of producing some or all of the biological effects similar to those of progesterone are called progestins (or progestogens).

Progestin
Originally, the crude hormone of the corpus lutetium of the ovary; it has since been isolated in pure form and is now known as progesterone. The generic term for any substance, natural or synthetic, that effects some or all of the biological changes produced by the hormone progesterone. See *progesterone.*

Progestin/estrogen replacement therapy (PERT)
The use of estrogen combined with progestin for the treatment of menopausal symptoms, e.g., hot flashes, the prevention of heart disease, and/or the prevention of osteoporosis; progestin opposes the carcinogenic effects of estrogen on the endometrium.

Progestogen
See *progestin.*

Prospective study
An epidemiologic study in which data are gathered after a hypothesis has been generated and the study approved. In a prospective study, the investigator first identifies the subjects and then follows them over time for development of disease. Compare *retrospective study.*

Provera
Wyeth-Ayerst's brand of the progestin medroxyprogesterone acetate (MPA). The most commonly used progestin for HRT in the United States. See *progestin, progesterone.*

Quality-adjusted life-year (QALY)
In cost-effectiveness analysis, a measure of health impact used to compare the benefit or effectiveness of alternative health interventions, such as the value of an extra year of life gained through kidney transplantation versus dialysis for patients with end stage renal disease; involves some degree of arbitrary valuation and weighting of different conditions.

Quantitative computerized tomography (QCT)
A bone densitometry technique similar to DEXA which measures the central, trabecular portion of the vertebral body, the spongiosa. Techniques have been developed to allow for quantitative measurement on most commercially available CT scanners.

Radiographic densitometry
Noninvasive measurement of bone mass in vivo was first performed by quantifying radiographs with an optical densitometer. The film density over the bone is compared to that over the soft tissue, and the resultant absorption is related to that obtained over a series of standards with known mineral content. Because of technical errors related to the polychromate nature of the radiation source and differences in x-ray film characteris-

tics, this technique has many errors and is rarely used clinically today.

Radiogrammetry

X-rays of the hand and radius, using fine grain industrial film, have been used to measure the cortical thickness of these tubular bones as an indicator of cortical bone mass. Although the proximal radius and ulna and the six middle metacarpal of both hands have been used, the mid-shaft of the second metacarpal is the usual measurement site.

Radius

The bone on the outer or thumb side of the forearm. The **distal radius is** the end of the radius bone adjacent to the wrist. The **proximal radius** is the end of the radius adjacent to the elbow.

Random allocation

In a randomized clinical trial, allocation of individuals to treatment groups such that each individual has an equal probability of being assigned to any group.

Randomized clinical trial (RCT) (also called randomized controlled clinical trial or controlled clinical trial)

In epidemiology, a clinical trial of a prophylactic, diagnostic, or therapeutic agent, device, regimen, procedure, etc. in which human (or animal) subjects are randomly allocated into groups, usually called "the experimental group" (in which subjects receive the treatment being studied) and "the control group" (in which subjects do not receive the treatment being studied), and outcomes are compared.

Recall bias

Bias caused by differences in abilities of two groups to remember exposure to suspected causative factors.

Recency

Time since last exposure to a suspected causative factor.

Regression analysis

A statistical procedure for determining the best approximation of the relationship between variables. Multiple regression analysis is a method for measuring the effects of several factors concurrently.

Relative risk

A measure of a relationship, defined as the chance of an outcome, such as breast cancer, among a group of persons having a suspected causative factor, divided by the chance of this outcome among a similar group without this suspect factor.

Reliability

The reproducibility of results over repeated measurements, and relates to the lack of random error over these repeated measurements. Reliability is a prerequisite to validity.

Retrospective study

An epidemiologic study in which data that are already available are analyzed to test a hypothesis (e.g., inferences about exposure to a possible causal factor are derived from data on subjects who already have the disease in question, compared to other subjects who do not have the disease).

Risk factor

An aspect of personal behavior or lifestyle, an environmental exposure, or an inborn or inheritance characteristic, which on the basis of epidemiologic evidence is known to be associated with health related conditions considered important to prevent.

Route of administration

In pharmacology, refers to the means by which a drug is administered: namely intravenous (injected into the bloodstream), inhalation (through the lungs), oral (through ingestion), and dermal (through the skin).

Secondary preventions

An intervention that strives to shorten the course of an illness by early identification and rapid intervention.

Selection bias

A distortion in the estimate of effect resulting from the manner in which subjects are selected for a study population.

Sensitivity
The percentage of all those who actually have the condition being tested who are currently identified as positive by the test.

Sensitivity analysis
In cost-effectiveness and cost-benefit analysis, an analysis of the effect of changes in key assumptions or uncertainties on the findings and outcome of the overall study.

Serum lipid profiles
A quantitative representation of the level of serum lipids.

Serum triglycerides
Esters formed from glycerol and one to three fatty acids; fats and oils are triglycerides.

Significance level
The significance level, or "p" value, is the probability of concluding that a relative risk is different from 1.0 when it is not. By convention, a difference in risk is said to be statistically significant if there is less than a five percent chance of making this type of error (i.e., $p < 0.05$). The significance can also be expressed as a confidence interval.

Single photon absorptiometry (SPA)
A bone densitometry technique that employs a sealed source of radioactive material that emits a single energy radiation (photon), and a detector that measures the amount of photons transmitted through bone and soft tissue. The radius and calcareous can be measured with this device.

Single photon x-ray absorptiometry (SXA)
A bone densitometry technique similar to SPA but using an x-ray source rather than a radioactive source. Both the radius and calcareous can be measured with this device.

Specificity
One measure of the validity (or accuracy) of a diagnostic or screening test: the percentage of all those who do not have the condition being tested or who are correctly identified as negative by the test. Operationally, it is the number of negative test results divided by the number of patients that actually have the disease (true-negatives divided by the sum of true-negatives plus false-positives). Compare *sensitivity.*

Statistically significant
The likelihood that an observed association is not due to chance. See *P value.*

Steroid hormone
Any of numerous hormones characterized by steroid structure (i.e., four carbon rings interlocked to forma hydrogenated cyclopentophenanthrene-ring system). Steroid hormones include the sex hormones estrogen, progestin, and androgen; they also include cortisone and adrenocortical hormones.

Steroids
Any of a class of compounds characterized by a polycyclic structure like that of the sterols and that usually include the sterols (e.g., cholesterol) and vitamin D, as well as many other naturally occurring compounds (e.g., bile acids).

Stratification
In randomized clinical trials, the categorization of individuals for the purpose of adjusting the groups to take into account unequal distribution of characteristics of prognostic importance. Stratification may be used during patient allocation, creating subgroups within which individuals are randomized to treatments; or stratification maybe applied during data analysis to statistically adjust for differences between the groups.

Stress incontinence
See *urinary stress incontinence.*

Stroke
Loss of sensation, movement, or function caused by a sudden interruption of the blood supply or a leakage of blood in the brain. This can be caused by heart failure, blockage of arteries (cerebral thrombosis or cerebral embolism), or hemorrhage in the brain.

Subcutaneous
Beneath the skin.

Subgroup analysis
A separate analysis performed on a subgroup of the population being studied to identify important differences in risk. Such differences in risk maybe

due to interactions of the purported causative factor with other risk factors for the disease.

Surgical menopause
Menopause following the surgical removal of the ovaries.

Symptomatology
The combined symptoms of a disease.

Synthetic calcitonin
A synthetically produced/manufactured form of the hormone calcitonin, a 32 amino acid polypeptide, one of the three calcium regulating hormones found in humans. The FDA has granted qualified approval for both natural and synthetic calcitonin for the treatment but not the prevention of osteoporosis.

Synthetic estrogen
A synthetically produced/manufactured estrogen product.

Systemic circulation
Channels through which nutrient fluids of the body flow: often restricted to the vessels conveying blood.

Testosterone
An androgen or steroid hormone secreted by the interstitial cells of the testes, which functions in the induction and maintenance of male secondary sex characteristics and affects sperm production; testosterone and its cypionate, enanthate, and propionate esters are used in palliative therapy in inoperable carcinoma of the female breast and certain gynecologic conditions.

Thromboembolitic disease
Disease related to blood vessel obstruction.

Thrombosis
The abnormal development of a blood clot (thrombus) inside an intact blood vessel, which can be life-threatening if it obstructs the blood supply to the brain (leading to stroke), heart (leading to myocardial infarction), the lungs (leading to pulmonary embolism), or other organs (leading to tissue damage or loss of function); the presence of such clots also raises the risk that part of the clot (an embolus) may break off and travel to a distant artery or vein, causing thrombophlebitis or deep vein thrombosis. Factors contributing to thrombosis include atherosclerosis, an increase in coagulation factors, or a deficiency of anticlotting factors in the blood.

Total cumulative exposure
The total dose, which is related both to the level and to the duration of exposure. For example, for estrogen replacement therapy, total dose is related to how much and for how long the estrogen is given.

Trabecular bone
See *cancellous bone.*

Transdermal
Through the skin.

Transmenopausal
Occurring across the time period of the menopause.

Treatment group
In a randomized clinical trial, the group receiving the treatment being evaluated for safety and efficacy. Also known as the experimental group. See *randomized clinical trial (RCT).*

Tumor
A new growth of tissue in which the multiplication of cells is uncontrolled and progressive. Also called neoplasm.

Ultrasound
Predictor of fracture risk using sound velocity and sound attenuation to measure both bone mass and altered bone architecture.

Unopposed estrogen
Estrogen used alone, without a progestin. Also known as estrogen replacement therapy (ERT).

Unopposed progestin
Progestin used alone. Progestins alone have been used to relieve menopausal symptoms.

Urinary bladder
The hollow, muscular organ that collects urine from the ureters and stores it until the urine is discharged through the urethra during urination.

Urinary incontinence
An involuntary loss of urine sufficient in quantity and/or frequency to be a social or health problem.

Urinary stress incontinence
Involuntary escape of urine due to strain on the orifice of the bladder, as in coughing or sneezing.

Urodynamics
A process that evaluates characteristics of the urine stream and the pelvic musculature, and the activity of the bladder.

Uterine prolapse
Descension of the uterus down into the vagina, caused by weakening of the support ligaments and muscles that hold the uterus in place.

Uterus
The hollow muscular organ in the female in which the fertilized ovum normally becomes embedded and in which the developing embryo and fetus are nourished. Its cavity opens into the vagina below and into a fallopian tube on either side.

Vagina
The canal in the female, from the vulva to the cervix uteri, that receives the penis in copulation and is the birth canal.

Vaginal atrophy
The wasting or diminution in size of the vagina.

Vaginismus
Painful, involuntary contraction or spasm of the muscles around the outer third of the vagina, interfering with sexual intercourse.

Validity
A measure of the extent to which an observed situation reflects the "true" situation.

Vertebra
In the human body, any of the 33 bones of the spinal column, comprising the 7 cervical, 12 thoracic, 5 lumbar, 5 sacral, and 4 coccygeal vertebrae.

Withdrawal bleeding
Bleeding, associated with hormone replacement therapy, caused by the sloughing of the endometrium due to withdrawal of estrogen stimulation.

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