Hormone Therapy To Prevent Disease and Prolong Life in Postmenopausal Women

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■ *Purpose:* To critically review the risks and benefits of hormone therapy for asymptomatic postmenopausal women who are considering long-term hormone therapy to prevent disease or to prolong life.

■ *Data Sources:* Review of the English-language literature since 1970 on the effect of estrogen therapy and estrogen plus progestin therapy on endometrial cancer, breast cancer, coronary heart disease, osteoporosis, and stroke. We used standard meta-analytic statistical methods to pool estimates from studies to determine summary relative risks for these diseases in hormone users and modified lifetable methods to estimate changes in lifetime probability and life expectancy due to use of hormone regimens.

■ *Results:* There is evidence that estrogen therapy decreases risk for coronary heart disease and for hip fracture, but long-term estrogen therapy increases risk for endometrial cancer and may be associated with a small increase in risk for breast cancer. The increase in endometrial cancer risk can probably be avoided by adding a progestin to the estrogen regimen for women who have a uterus, but the effects of combination hormones on risk for other diseases has not been adequately studied.

We present estimates for changes in lifetime probabilities of disease and life expectancy due to hormone therapy in women who have had a hysterectomy; with coronary heart disease; and at increased risk for coronary heart disease, hip fracture, and breast cancer.

■ *Conclusions:* Hormone therapy should probably be recommended for women who have had a hysterectomy and for those with coronary heart disease or at high risk for coronary heart disease. For other women, the best course of action is unclear.

[Note that sections in this review are numbered so that they can be identified with cross-references as supporting evidence for the Clinical Guideline, (Guidelines for Counseling Postmenopausal Women about Preventive Hormone Therapy), which also appears in this issue of Annals; *see pages 1038-1041—The Editors]*

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Our purpose is to quantify the risks and benefits of hormone therapy in asymptomatic postmenopausal women. Hormone therapy is defined as treatment with estrogen or a combination of estrogen plus progestin. Although hormone therapy has been shown to relieve postmenopausal vasomotor and genitourinary symptoms (1-3), we will not consider hormone treatment for symptomatic relief. We will critically review the risks and benefits of hormone therapy for a 50-year-old woman who is perimenopausal or recently postmenopausal and is considering long-term hormone therapy to prevent disease or prolong life. We will also consider how the risks and benefits of hormone therapy differ in women at risk for diseases affected by hormone therapy.

2.0 Methods

We reviewed the published English-language literature since 1970 reporting the effect of estrogen therapy and estrogen plus progestin therapy on endometrial cancer, breast cancer, coronary heart disease, osteoporosis, and stroke. We chose to assess end points that are major contributors to morbidity and mortality and that have been linked with hormone therapy. The findings of this literature review are outlined in Tables 1 through 5.

We used the meta-analytic statistical methods described by Greenland (4) to pool estimates from individual studies and to determine summary estimates of the relative risks for hormone use. Our aim was to provide the best relative-risk estimates for long-term use of standard-dose estrogen (equivalent to 0.625 mg of conjugated equine estrogen daily) and for long-term use of standard-dose estrogen plus a progestin (Appendix 1).

Using modified lifetable methods, we calculated the lifetime probability for a woman to develop endometrial cancer, breast cancer, coronary heart disease, hip fracture, and stroke; and the median life expectancy for a perimenopausal white woman (estimated to be 50 years old). We also estimated changes in lifetime probability and life expectancy due to use of hormone regimens (Appendix 2).

We did the same type of analysis for various hypothetical subgroups of white women: women who have had a hysterectomy; women with diagnosed coronary heart disease; women at increased risk for coronary heart disease; women at increased risk for hip fracture; and women at increased risk for breast cancer. We repeated these analyses among similar subgroups of black women using age- and race-specific disease incidence and mortality data (*see* Appendix 2).

We also reviewed the available literature to address the effects of hormone regimens on serum lipoproteins, incidence of endometrial hyperplasia, incidence and pattern of uterine bleeding, sexual function, urinary function, quality of life, incidence and severity of adverse effects, and the need for invasive monitoring procedures.

3.0 Results

3.1 Endometrial Cancer

A 50-year-old white woman has a 2.6% lifetime probability of developing cancer of the endometrium. Be-

Table 1. Postmenopausal Hormone Use and Endometrial Cancer

Reference (Year)	Unopposed Estrogen			Estrogen and Progestin
	Ever Use Relative Risk	Duration of Use		Ever Use Relative Risk
		Years of Use	Relative Risk	
Case control				
Smith (188) (1975)	4.5*			
Ziel (12) (1975)	7.6*	>7	13.9*	
Mack (5) (1976)	8.0*	>8	8.5*	
Gray (6) (1977)	2.1*	≥10	11.6*	
McDonald (7) (1977)	0.9	≥3	7.9*	
Horwitz (191) (1978)	12.0*‡ 2.3*¶			
Hoogerland (13) (1978)	2.2*	≥10	6.7*	
Wigle (14) (1978)	2.5*	≥5	5.2*	
Antunes (22) (1979)	5.5*	>5	15.0*	
Weiss (8) (1979)	4.5*	>20	8.3*	
Shapiro (15) (1980)	3.9*	≥5	6.0*	
Hulka (9, 23) (1980a,b)	1.4	>3.5	3.6*	
Jelovsek (16) (1980)	2.4*	>10	2.6*	
Salmi (192) (1980)	0.4*			
Spengler (17) (1981)	2.9*	>5	8.6*	
Stavraky (173) (1981)	4.3*	≥10	14.4*	
Kelsey (25) (1982)	1.6*	>10	2.7*	
Henderson (194) (1983)	1.8	≥2	3.1*	
La Vecchia (195) (1984)	1.6*	>2	2.1*	
Shapiro (18) (1985)	3.5*	≥10	10.0*	
Buring (10) (1986)	2.4*	≥10	7.6*	
Ewertz (28) (1988)	4.7*			
Rubin (29) (1990)	1.9*	>6	3.5*	
Voigt (32) (1991)	3.1*	≥3	5.7*	1.3
Uncontrolled cohort				
Hoover (196) (1976)	2.3*			
Vakil (62) (1983)	1.3			
Hunt (197) (1987)	2.8*			
Cohort				
Hammond (198) (1979)	5.8*			†
Gambrell (31) (1980)	1.4			0.2*
Lafferty (204) (1985)	3.2			
Petitti (80) (1987)	2.6			
Ettinger (30) (1988)	7.7*			
Paganini-Hill (11) (1989)	10.0*	≥15	20.0*	
Persson (20) (1989)	1.4	≥6	1.8*	0.9
Randomized, controlled trial				
Nachtigall (64) (1979)				†

* $P \leq 0.05$.
† No cancers observed in the estrogen plus progestin group.
‡ Other gynecologic cancer controls.
¶ Surgery for benign condition controls.

cause endometrial cancer is usually curable, the probability of dying of endometrial cancer is much less—about 0.3%. The median age at which endometrial cancer develops is 68 years.

Estrogen Therapy and Endometrial Cancer

Since 1970, at least 35 epidemiologic studies have examined the association of exogenous estrogen treatment and cancer of the endometrium (Table 1). The overwhelming majority of these studies shows a significantly increased risk for endometrial cancer in women who have taken estrogen (Table 1). The pooled estimate of the relative risk for endometrial cancer in women who have ever used estrogen compared with those who never used estrogen is 2.31 (95% CI, 2.13 to 2.51). In the dosage range commonly prescribed (0.3 to 2.5 mg/d of conjugated estrogens), the risk for endometrial cancer is elevated for all doses and increases with increasing dose (5-11).

Risk for endometrial cancer increases with increasing duration of estrogen use (5, 7, 9-20). The pooled estimate from the studies that provided data on endometrial cancer among women who used estrogen 8 years or more compared with those who never used estrogen is 8.22 (CI, 6.25 to 10.81). This estimate may be somewhat high because some long-term users in these studies were taking high-dose estrogen. Only two studies (5, 10) provide information on the risk for endometrial cancer in women who took 0.625 mg of conjugated estrogen for at least 5 years and show risk ratios of 4.8 and 4.3.

Although risk for developing endometrial cancer in estrogen users is significantly elevated, the risk for dying from this disease among estrogen users may not be equally increased. An increased incidence of endometrial cancer in the United States in the 1970s clearly paralleled increasing estrogen use, but mortality from endometrial cancer did not (21). The reason for this

finding is not entirely clear but may be because endometrial cancers associated with estrogen use are not as aggressive as spontaneously occurring cancers or because women who take estrogen are likely to have their tumors discovered at an early stage. Estrogen may cause early bleeding from endometrial tumors and women taking estrogen often have regular examinations and endometrial tissue sampling. At diagnosis, endometrial cancers in women who have used estrogen are generally of earlier stage and lower grade and show less myometrial invasion than tumors in women who have not used estrogen (5, 7, 10, 16, 22-25). As would be expected from the lower grade and earlier stage of cancers in estrogen users, survival is better than in nonusers with the disease (24, 26, 27). However, several studies have shown increased risk for late-stage, high-grade invasive tumors (18, 28, 29) and a nonsignificant increased risk for endometrial cancer death in estrogen users (5, 11, 30). Study findings are too inconsistent to permit calculation of a summary relative risk for dying of endometrial cancer among estrogen users.

Estrogen plus Progestin Therapy and Endometrial Cancer

Five studies have examined the effect of estrogen plus progestin therapy on endometrial cancer risk (*see* Table 1). None of these studies shows a significantly increased risk compared with nonusers, and one showed a significantly decreased risk for endometrial cancer among women using estrogen plus a progestin (31). The best available epidemiologic evidence is from one case-control study that showed no increased risk for endometrial cancer when progestins were used with estrogen for at least 10 days per month (32). The relative risks from these studies are too variable to permit calculation of a pooled estimate of relative risk.

Additional evidence that progestins prevent the increased risk for endometrial cancer associated with unopposed estrogen treatment is based on studies of endometrial hyperplasia, which may be a precursor of endometrial cancer (33, 34). Endometrial hyperplasia occurs in 20% to 40% of women taking unopposed estrogens (35) and can be prevented by adding a progestin to the estrogen regimen (35, 36). In addition, endometrial hyperplasia that develops in women taking unopposed estrogen can often be successfully treated with progestins (37-39).

Summary of the Effect of Hormone Therapy on Endometrial Cancer Risk

The evidence that unopposed estrogen therapy increases the risk for endometrial cancer is extensive, strong, and consistent. On the basis of pooled data, our model of the risks and benefits of estrogen therapy uses a relative-risk estimate of 8.22 for endometrial cancer among women with long-term estrogen use.

Risk for death from endometrial cancer is probably not increased as dramatically in estrogen users as risk for developing this cancer, but an assumption that no increase in risk of death exists is not justified; therefore we have used a relative risk of 3.0 in our model for endometrial cancer death due to long-term estrogen use.

Histologic and clinical data, as well as limited epidemiologic data, suggest that the addition of a progestin to the estrogen regimen prevents the increase in endometrial cancer risk associated with estrogen therapy. Our model uses a relative risk of 1.0 for endometrial cancer for long-term users of combination hormone therapy.

3.2 Breast Cancer

A 50-year-old white woman has a 10% lifetime probability of developing and a 3% probability of dying of breast cancer. The median age at which breast cancer develops is 69 years.

Estrogen Therapy and Breast Cancer

At least 39 epidemiologic studies of estrogen therapy and breast cancer risk have been done since 1970 (*see* Table 2). The findings of these studies are not consistent. Three recently published meta-analyses based on the data from these studies found no increased risk for breast cancer in women who ever took estrogen (generally $\leq$ 5 years of use) compared with nonusers (40-42). Our estimate of the summary relative risk for breast cancer among "ever-users" compared with those who never used estrogen is 1.01 (CI, 0.97 to 1.05).

There is no clear evidence that risk for breast cancer increases with increasing doses of estrogen (43-49) or different treatment regimens (48).

Those studies that evaluated the effect of long-term estrogen use have also had conflicting results. Many show a small increase in risk among women who took estrogen for the longest duration (43, 44, 46, 48-54, 69, 197, 225), whereas others do not (47, 55-59, 68). A recent meta-analysis that pooled duration response slopes from 16 case-control studies that provided information on risk for breast cancer by duration of estrogen use reported a summary risk estimate of 1.3 (CI, 1.2 to 1.6) for women who had used estrogen for at least 15 years compared with nonusers (42). We pooled estimates from case-control and cohort studies that provided data on risk of breast cancer in women who used estrogen for 8 years or more compared with nonusers and calculated a summary relative risk of 1.25 (CI, 1.04 to 1.51). This estimate may be too high due to surveillance bias in women who take estrogen or too low if estrogen treatment has been withheld from women at high risk for breast cancer (60).

The few studies that have examined risk for death from breast cancer among estrogen users are inconclusive. Three studies suggested a reduced risk for breast cancer death among estrogen users, but none included internal controls, and the total number of breast cancer deaths was small (61-63). The Nurses' Health Study reported a relative risk of 1.11 (CI, 0.67 to 1.84) for breast cancer death among estrogen users. No evidence on the effect of long-term estrogen use on risk for death from breast cancer is available.

Estrogen plus Progestin Therapy and Breast Cancer

Only six studies have examined the effect of estrogen plus progestin on breast cancer risk, and the findings of these studies are inconsistent (*see* Table 2). Because adding a progestin to the estrogen regimen is protective for endometrial cancer, it has been suggested that add-

Table 2. Postmenopausal Hormone Use and Breast Cancer

Reference (Year)	Unopposed Estrogen			Estrogen and Progestin		
	Ever Use Relative Risk	Duration of Use		Ever Use Relative Risk	Duration of Use	
		Years of Use	Relative Risk		Years of Use	Relative Risk
Case-control						
Boston Collaborative Drug Surveillance Program (132) (1974)	1.0					
Mack (209) (1975)	1.6					
Casagrande (211) (1976)	1.2					
Sartwell (55) (1977)	0.8	≥5	0.6			
Wynder (212) (1978)	1.1					
Ravnihar (215) (1979)	1.0					
Ross (43) (1980)	1.1	1500†	1.9*			
Jick (216) (1980)	1.9*					
Hoover (44) (1981)	1.4	≥5	1.7*			
Kelsey (45) (1981)	0.9	5% less risk/y use				
Hulka (46) (1982)	1.4	10+	1.7			
Sherman (218) (1983)	0.6*					
Hiatt (56) (1984)	0.7	5+	0.8			
Horwitz (219) (1984)	0.9					
Kaufman (47) (1984)	0.6	≥10	0.5			
La Vecchia (50) (1986)	1.8*	>2	2.0*			
McDonald (57) (1986)	0.7	≥6	0.7			
Nomura (58) (1986)	0.9	>5	1.0			
Brinton (48) (1986)	1.0	20+	1.5			
Wingo (49) (1987)	1.0	≥20	1.8			
Ewertz (51) (1988)	1.2	>12	1.6*	1.4*		
Rohan (59) (1988)	1.0	≥2	0.9			
Palmer (69) (1991)	1.0	≥15	1.5	0.6		
Kaufman (68) (1991)	1.2	10 to 14	1.0	1.7		
Uncontrolled cohort						
Hoover (222) (1976)	1.3					
Byrd (61) (1977)	1.4					
Vakil (62) (1983)	0.6*					
Hunt (197) (1987)	1.6*	≥10	3.1*			
Cohort						
Bland (224) (1980)	0.4					
Hammond (198) (1979)	1.0					
Thomas (225) (1982)	1.8*	≥5	1.9			
Gambrell (65) (1983)	0.4*			0.2*		
Lafferty (204) (1985)	0.2					
Petitti (80) (1987)	0.8					
Dupont (227) (1989)	0.5*					
Bergkvist (52) (1989)	1.1*	≥9	1.8*	§	6 to 9	4.4
Mills (53) (1989)	1.4*	>10	1.5			
Colditz (54) (1990)	1.4*‡	>15	1.2			
Randomized, controlled trial						
Nachtigall (64) (1979)				‖		

* $P \leq 0.05$.
† TMD = average milligram per day multiplied by months of estrogen use.
‡ Relative risk for current estrogen use.
§ Not reported.
‖ No cancers were observed in the estrogen plus progestin group.

ing a progestin to the estrogen regimen might also be protective for breast cancer. One small, randomized controlled trial (168 participants) found a nonsignificant decrease in risk for breast cancer in women treated with the combination regimen compared with untreated women (64). The only study (65) that showed a statistically significant decrease in risk for breast cancer in women treated with estrogen plus progestin is flawed by lack of adjustment for age or other potential confounders and by other methodologic problems (66).

Some concern exists that adding progestin to the estrogen regimen might increase the risk for breast cancer. In endometrial cells, mitotic rate increases under the influence of estrogen during the follicular phase of the menstrual cycle, then decreases with increasing levels of progesterone during the luteal phase. In contrast, increasing levels of progesterone in the luteal phase result in additional increases in mitotic activity in breast cells, suggesting that combination regimens may increase rather than decrease risk for breast cancer (67). Two large case-control studies showed an increased risk among women who had ever taken estrogen plus a progestin (51, 68), whereas a third study did not (69). The only study that examined the effect of long-term combination hormone use on breast cancer reported a nonsignificant fourfold increase in risk among women who had used estrogen plus progestin for 6 years or more (52). The variability in these studies prohibits cal-

Table 3. Postmenopausal Hormone Use and Coronary Heart Disease

Reference (Year)	Unopposed Estrogen			Estrogen and Progestin
	Ever Use Relative Risk	Duration of Use		Ever Use Relative Risk
		Years of Use	Relative Risk	
Case-control				
Rosenberg (238) (1976)	1.0*			
Talbott (83) (1977)	0.3*†			
Jick (70) (1978)	4.2*†			
Pfeffer (237) (1978)	0.9			
Rosenberg (113) (1980)	1.0*	≥5	0.6*	
Adam (77) (1981)	0.6†	>4	1.0†	
Bain (229) (1981)	0.8			
Ross (81) (1981)	0.5†‡			
Szklo (241) (1984)	0.6			
La Vecchia (233) (1987)	3.0*			
Beard (230) (1989)	0.6			
Croft (231) (1989)	0.8			
Thompson (114) (1989)	1.1§			1.2§
Cross-sectional				
Gruchow (96) (1988)	0.6‡‖			
	0.4‡¶			
Sullivan (240) (1988)	0.6‡			
McFarland (235) (1989)	0.5‡			
Uncontrolled cohort				
Byrd (61) (1977)	0.4†‡			
MacMahon (234) (1978)	0.3	≥15	0.8	
Hunt (63) (1990)	0.4‡			
Cohort				
Hammond (117) (1979)	0.3†‡			
Lafferty (204) (1985)	0.2†			
Wilson (73) (1985)	1.9‡			
Bush (78) (1987)	0.4‡			
Petitti (80) (1987)	1.3			
Criqui (79) (1988)	1.0*			
Avila (228) (1990)	0.7*	≥1	0.3*	
Persson (101) (1990)	0.8‡			0.5‡
Sullivan (82) (1990)	0.2*‡			
Henderson (76) (1991)	0.7†‡	≥15	0.5 ‡	
Stampfer (85) (1991)	0.6*‡			
Wolf (84) (1991)	0.7‡			
Randomized, controlled trial				
Nachtigall (64) (1979)				0.3†

* Current estrogen use.
† The relative risk or P value or both are estimated from data provided in the published study.
‡ $P \leq 0.05$.
§ End points include both stroke and myocardial infarction.
‖ Moderate versus low coronary occlusion score.
¶ Severe versus low coronary occlusion score.

culation of a pooled risk estimate of the effect of long-term estrogen plus a progestin on breast cancer.

Summary of the Effect of Hormone Therapy on Breast Cancer Risk

A large body of data exists concerning the effect of estrogen therapy on risk for breast cancer, but the results are not consistent. Although there appears to be no increased risk among short-term users of estrogen, the risk for breast cancer may increase slightly among long-term users. On the basis of pooled data, our model uses a relative risk of 1.25 for developing and of dying of breast cancer in women treated with long-term estrogen therapy.

Evidence concerning the effect of estrogen plus progestins on breast cancer risk is limited, but there is some reason to worry about increased risk with long-term use. The inconsistency of this data prevents calculation of a pooled estimate of the effect of estrogen plus progestin on breast cancer risk.

3.3 Coronary Heart Disease

Coronary heart disease (CHD) is the leading cause of death among postmenopausal women. A 50-year-old white women has a 46% lifetime probability of developing and a 31% probability of dying of heart disease. Death from CHD occurs at a median age of 74 years.

Estrogen Therapy and Coronary Heart Disease

Since 1970, at least 32 epidemiologic studies have evaluated the relation between noncontraceptive estrogen use and CHD (Table 3). Most of these studies found a lower risk for CHD among estrogen users compared with nonusers. A reduction in risk has been reported for a variety of end points, including fatal coro-

nary heart disease, fatal and nonfatal myocardial infarction, fatal and nonfatal cardiovascular disease, coronary stenosis, and sudden death. The few studies that suggest an increased risk for CHD in estrogen users are characterized by relatively small numbers of estrogen users and various methodologic problems (70-73).

Our pooled estimate of the relative risk for CHD in women who have ever used estrogen compared with those who never used estrogen is 0.65 (CI, 0.59 to 0.71). Two other meta-analyses using slightly different methods reported summary risk estimates for CHD among estrogen users of 0.55 (74) and 0.58 (75).

The dose of estrogen used in most of the studies that have shown protection from CHD among users was equivalent to 0.625 to 1.25 mg of oral conjugated estrogen daily, but data are inadequate to allow evaluation of dose-response. Prolonged duration estrogen treatment may be necessary to achieve optimal benefit because CHD is a chronic and progressive disease. One study reported a lower risk for CHD among women using estrogen for 15 or more years (relative risk, 0.5) than for use of less than 3 years (relative risk, 0.9) (76), but the data are insufficient to determine if protection against CHD increases with increasing duration of estrogen use.

Studies that have assessed risk for fatal heart disease show a reduction in death from heart disease among women who take estrogen (76-84). Six of these 10 studies found a statistically significant reduction of fatal heart disease in estrogen users (76, 78, 81, 82, 84, 85). Our pooled estimate of the relative risk for CHD death among ever-users of estrogen compared with nonusers is 0.63 (CI, 0.55 to 0.72).

Some evidence shows that the protective effect of estrogen is stronger in women who already have CHD than in healthy women. In a group of women with angiographically diagnosed CHD, risk for recurrent disease was reduced 84% (82).

Estrogen plus Progestin and Coronary Heart Disease

Estrogen therapy has been shown to reduce serum low-density lipoprotein (LDL)-cholesterol and increase serum high-density lipoprotein (HDL)-cholesterol in a dose-dependent fashion (86-90). Oral estrogen (0.625 mg oral conjugated estrogen or the equivalent daily) decreases LDL about 10% to 15% and increases HDL about 10% to 15% (86). Progestins attenuate the beneficial effect of estrogen on lipoproteins (3, 91-94), raising the concern that the addition of progestin might reduce the cardioprotective benefits of estrogen therapy. The extent to which the beneficial effect of estrogen on lipoproteins is reversed depends on the type, dose, and duration of progestin added (3, 93-95).

Changes in lipoproteins, however, are probably not the only mechanism by which estrogen reduces CHD risk. In two studies that determined the effect of estrogen on CHD risk after adjusting for changes in lipids, only 25% to 50% of the risk reduction conferred by estrogen treatment was accounted for by changes in lipids (78, 96). Specific receptors for estrogen are located in the muscularis of arteries (97), suggesting that estrogen might directly affect the vasculature. Treatment with estrogen might also reduce the risk for coronary thrombosis and infarction by favorably altering thrombotic mediators. Estrogen increases production of prostacyclin in the endothelium of blood vessels and decreases production of thromboxane A_2 by platelets, reducing platelet adhesiveness (98). Results of recent experiments in postmenopausal female monkeys fed an atherogenic diet found that estrogen favorably changed lipoproteins and protected against the development of atherosclerosis. The combination of estrogen and progesterone did not produce a beneficial effect on lipoproteins, but the combination protected against the development of atherosclerosis as well as estrogen alone (99, 100).

Only three studies have assessed the effect of treatment with estrogen plus a progestin on CHD risk in women (*see* Table 3). One case control study reported a slight increase in risk for CHD in women treated with estrogen plus a progestin, but the end point included stroke as well as myocardial infarction (114). One small, randomized controlled trial of 168 women found a nonsignificant reduction in relative risk for CHD in women taking estrogen plus a progestin (relative risk, 0.3) (64). Preliminary results from a study of a large cohort of women in Sweden suggested a statistically significant reduction in risk for CHD among postmenopausal women who used a combination of estrogen and norgestrel (relative risk, 0.5) and the degree of protection appeared to be as great as that observed for women taking estrogen alone (101).

Summary of the Effects of Hormone Treatment on Coronary Heart Disease

There is extensive and consistent observational evidence that estrogen use reduces risk for CHD about

Table 4. Postmenopausal Hormone Use and Hip Fracture

Reference (Year)	Unopposed Estrogen		
	Ever Use	Duration of Use	
	Relative Risk	Years of Use	Relative Risk
Case-control			
Hutchinson (125) (1979)	0.2*†	>5	0.2†‡
Weiss (102) (1980)	0.4*‡§	≥10	0.5*
Johnson (242) (1981)	0.7		
Paganini-Hill (245) (1981)	0.7†	>5	0.4*
Kreiger (244) (1982)	0.4*†		
Williams (248) (1982)	0.4*†		
Cohort			
Hammond (117) (1979)	0.5*†		
Ettinger (124) (1985)	0.4*†		
Kiel (243) (1987)	0.6*		
Naessén (246) (1990)	0.8*‖		
Paganini-Hill (247) (1991)	1.0	≥15	0.9

* $P \leq 0.05$.

† The relative risk or P value or both are estimated from data provided in the published study.

‡ Risk estimate for hip and distal radius fractures combined.

§ Current estrogen use.

‖ 41% of women < 60 years and 20% of women > 60 years used combined estrogen plus progestin regimen. Cases are compared with population-based fracture rates in Uppsala, Sweden.

35%. The reduction in risk may be greater in women who already have CHD. On the basis of pooled data, we used a relative-risk estimate of 0.65 in our model for developing and dying of CHD among women treated with estrogen.

Compared with women who do not take hormones, risk for CHD is probably reduced among women taking estrogen plus a progestin, but data are inadequate to determine the magnitude of the benefit.

3.4 Osteoporotic Hip Fracture

A 50-year-old white woman has a 15% lifetime probability of suffering a hip fracture and a 1.5% probability of dying of a hip fracture. The median age at first hip fracture is 79 years.

Estrogen Therapy and Hip Fracture

At least 11 epidemiologic studies of estrogen and hip fracture have been done since 1970. All but one of these studies report a reduction in risk for hip fracture among estrogen users compared with nonusers (Table 4). The pooled estimate of the relative risk for hip fracture comparing ever-users of estrogen with nonusers is 0.75 (CI, 0.68 to 0.84).

The dose of estrogen used in most of the studies that have shown protection from hip fracture among users was equivalent to 0.625 mg of conjugated estrogen daily, but the data are inadequate to evaluate dose-response effect. Some evidence suggests that the risk for hip fracture decreases with increasing duration of estrogen use. In one study, women who had used estrogen for 1 to 2 years were found to have a relative risk for hip or lower-forearm fracture of 0.8, whereas those who had taken estrogen for 10 or more years had a relative risk of 0.5 (102). When estrogen therapy is discontinued, bone loss occurs at an accelerated early postmenopausal rate (103-105), suggesting that estrogen therapy should be continued for a prolonged period. Among women who discontinue estrogen therapy, risk for fracture of the hip or lower forearm may return to near baseline (relative risk, 0.8 to 1.0) 6 or more years after cessation of therapy (102).

No data exist concerning risk for death from hip fracture among estrogen users.

Table 5. Postmenopausal Hormone Use and Cerebrovascular Disease

Reference (year)	Unopposed Estrogen		
	Ever Use	Duration of Use	
	Relative Risk	Years of Use	Relative Risk
Case-control			
Pfeffer (112) (1976)	1.1		
Rosenberg (252) (1980)	1.2		
Adam (77) (1981)	0.6†		
Uncontrolled cohort			
Byrd (61) (1977)	0.5†		
MacMahon (234) (1978)	0.8	15	1.7
Hunt (63) (1990)	0.5*		
Cohort			
Hammond (117) (1979)	0.2*†		
Petitti (134) (1979)	1.2†‡		
Lafferty (204) (1985)	§		
Wilson (73) (1985)	2.3*		
Bush (78) (1987)	0.4		
Boysen (249) (1988)	1.0†		
Henderson (76) (1991)	0.6*	≥15	0.5*
Stampfer (85) (1991)	1.0‡		
Finucane (116, 250) (1992)	0.7*		

* $P \leq 0.05$.

† The relative risk or P value or both are estimated from data provided in the published study.

‡ Current estrogen use.

§ No cerebrovascular events observed in the estrogen-treated group.

Estrogen plus Progestin Therapy and Hip Fracture

No studies have yet been done on the effect of estrogen plus progestin on risk for hip fracture. In a large Swedish cohort study (246), approximately 30% of the women took estrogen plus a progestin, but the risk for women who used the combined regimen was not analyzed separately. Several studies have found that estrogen plus progestin regimens prevent bone loss (106-108) and may even promote new bone formation (104, 105, 109-111).

Summary of the Effect of Hormone Therapy on Hip Fracture Risk

Limited but consistent observational evidence shows that estrogen therapy reduces the risk for hip fracture in postmenopausal women by about 25%. On the basis of pooled results, we used a relative risk of 0.75 for developing and dying from hip fracture for estrogen users compared with nonusers.

Although evidence from studies of hip fracture in women is limited, estrogen plus progestin therapy is probably at least as effective as unopposed estrogen in preventing hip fracture. Thus, in our model, we have used a relative-risk estimate of 0.75 for developing and dying of hip fracture among women treated with combination hormones compared with nonusers.

3.5 Stroke

A 50-year-old white woman has a 20% lifetime probability of developing and an 8% probability of dying of stroke. The median age of death from stroke is 83 years.

Estrogen Therapy and Stroke

Since 1970, at least 15 studies have evaluated the effect of estrogen use on stroke risk in women. The findings of these studies are not consistent. Some show a slightly increased risk for stroke among estrogen users (73, 112, 134, 252), whereas others find a slightly decreased risk (Table 5). Our pooled estimate of the relative risk for stroke among estrogen users is 0.96 (CI, 0.82 to 1.13).

Information on the effect of dose and duration of estrogen use on stroke risk is limited and inconsistent (76, 234). Studies that have assessed death from stroke consistently show a decreased risk among estrogen users (76-78, 80, 116, 250).

Estrogen plus Progestin Therapy and Stroke

Some of the studies of stroke included women who took estrogen plus a progestin, but risk for women who used the combined regimen was not analyzed separately (63, 117). No other epidemiologic data exist concerning the effect of estrogen plus progestin therapy on risk for stroke in women.

Summary of the Effects of Hormone Therapy on Stroke

The evidence is not convincing that estrogen either increases or decreases risk for stroke, and there is no information on the effect of estrogen plus progestin regimens on stroke risk in women. In our model, we used the pooled relative risk of 0.96 for stroke among estrogen users and among estrogen plus progestin users.

4.0 Other Effects of Hormone Therapy

Many effects of hormone therapy other than on risk for endometrial and breast cancer, CHD, hip fracture, and stroke have been investigated. Although these do not substantially affect life expectancy, they may influence the decision about taking hormones or which hormone regimen to use.

4.1 Other Effects of Estrogen Therapy

In women with a uterus, standard-dose estrogen used alone causes endometrial hyperplasia in about 5% to 25% of women per year (36, 118-121) and irregular vaginal bleeding in about 35% to 40% of women per year (36,119). The frequency of irregular bleeding may decrease with increasing age or years since menopause (30).

Estrogen therapy favorably alters the lipoprotein profile. Standard-dose estrogen (0.625 mg conjugated estrogen or equivalent) increases HDL by about 10% to 15% and reduces LDL by about 10% to 15% (89, 94, 122, 123).

In addition to reducing the risk for hip fracture, estrogen therapy reduces risk for vertebral and wrist fractures (102, 124-127). Although these fractures are not associated with increased mortality (128), they may cause significant morbidity, including pain, loss in height, and development of a "dowager's hump" (126).

Blood pressure generally does not change with estrogen therapy or may be somewhat reduced in both normotensive and hypertensive women (129, 130). In a small percentage of women, however, blood pressure may increase after beginning estrogen therapy (129, 130). Thrombosis is a recognized complication of oral contraceptive use, suggesting that estrogen therapy might also increase risk. However, no epidemiologic evidence exists that standard doses of estrogen increase the risk for thrombosis (64, 131-134). Estrogen treatment is associated with an approximately twofold increased risk for gallbladder disease, which may require cholecystectomy (132, 135) but does not commonly cause death.

No data are available to determine if estrogen therapy might prevent the development of urinary and sexual dysfunction that occurs as postmenopausal women age. Estrogen therapy may improve symptoms of urinary incontinence, frequency, and urgency (136-138) and increases urethral pressures (139, 140). Other objective measures of urinary function do not appear to improve with therapy (141, 142). Evidence concerning the effect of hormone therapy on sexual function is conflicting. Some studies have shown improvement in sexual desire and enjoyment among postmenopausal women treated with hormones (143, 144), whereas others have not (145, 146). Limited evidence suggests that estrogen therapy may improve mood and mental function, even in asymptomatic postmenopausal women (147).

It has been suggested that the progressive decrease in skin thickness and loss of skin collagen that occurs in women after the menopause can be prevented with estrogen therapy (148-153), but controlled trials of the effect of estrogen on skin are lacking.

Estrogen can cause unpleasant side effects that are dose-dependent such as bloating, breast tenderness, and headache. Side effects occur in approximately 5% to 10% of women taking standard-dose estrogen (154, 155), but most of these side effects are mild and do not require discontinuation of medication.

Table A. Relative Risk of Selected Conditions for a 50-Year-Old White Woman Treated with Long-Term Hormone Replacement

Condition	Relative Risk*	
	Estrogen Therapy	Estrogen plus Progestin
	%	
Coronary heart disease	0.65	0.65 to 0.80
Stroke	0.96	0.96
Hip fracture	0.75	0.75
Breast cancer	1.25	1.25 to 2.00
Endometrial cancer	8.22	1.00

* "Best" estimates of the relative risk for developing each condition in long-term hormone users compared with nonusers. These estimates were used in our model of the risks and benefits of hormone therapy. The same relative-risk estimate was used for dying of each condition in long-term users compared with nonusers except for endometrial cancer, where a relative risk of 3.0 was used.

4.2 Other Effects of Estrogen plus Progestin Therapy

The only proven rationale for adding a progestin to the estrogen regimen is to prevent the increased risk for endometrial cancer associated with estrogen treatment. The efficacy of progestins in preventing development of endometrial hyperplasia in women treated with estrogen has been used as a surrogate measure of efficacy in preventing endometrial cancer. Cyclic progestin regimens using 10 mg of medroxyprogesterone acetate (MPA) or equipotent progestin daily for 10 to 14 days per month have been shown to prevent development of endometrial hyperplasia (156, 157). While there is less evidence, cyclic regimens using 5 mg of medroxyprogesterone acetate also appear to be similarly protective (36). A continuous progestin regimen using 2.5 mg of medroxyprogesterone acetate daily with estrogen has also been shown to prevent endometrial hyperplasia and produce atrophic endometrium (93, 158-160). Other regimens, such as 10 mg of medroxyprogesterone acetate

(or equivalent) given daily for 10 days every third month, are presently being evaluated.

Predictable endometrial withdrawal bleeding occurs after stopping progestins in 50% to 80% of women taking cyclic regimens but becomes less prevalent after several years of treatment (36). Unpredictable bleeding occurs in 30% to 50% of women in the first 3 to 6 months of treatment with continuous regimens, but by 8 to 12 months of treatment almost all treated women have developed endometrial atrophy and do not bleed (155, 158-168).

Long-term, randomized comparisons of the effect on lipoproteins of various estrogen plus progestin regimens have not been reported, but such a trial (the Postmenopausal Estrogen/Progestin Interventions Trial) is presently underway. Progestins tend to produce changes in the lipid profile that would be expected to increase CHD risk (decreased HDL and increased LDL). These changes appear to be dose- and duration-dependent (91, 92). Cyclic use of 10 mg of medroxyprogesterone acetate for 10 days per month has substantially more adverse effect on lipoproteins than use of 5 mg of medroxyprogesterone acetate for 10 days per month (3, 94). Preliminary comparisons of the effect on lipids of continuous low-dose medroxyprogesterone acetate (2.5 mg daily) and cyclic low-dose medroxyprogesterone acetate (5 mg for 10 days per month) suggest that the cyclic regimen is associated with a slightly greater increase in HDL and decrease in LDL than the continuous regimen (169).

Estrogen plus progestin therapy has been shown to prevent vertebral fractures in women with osteoporosis, reducing risk about 60% (127). There are few data concerning the effect of added progestins on gallbladder disease, blood pressure, thromboembolism, urinary function, or mood. Some studies suggest that added progestins decrease the beneficial effects of estrogen on sexual function (143).

Therapy with progestins may cause unpleasant side effects such as breast tenderness, bloating, irritability, and depression (170). Such adverse effects may vary somewhat depending on the type of progestin used (170) and are dose related (171). Side effects appear to be less problematic in women taking low-dose daily progestins and in those taking natural progesterone (171, 172).

Table B. Lifetime Probabilities of Selected Conditions for a 50-Year-Old White Woman with Hysterectomy Treated with Long-Term Hormone Replacement

Variable	Lifetime Probability*	
	No Treatment	Estrogen
Coronary heart disease, %	46.2	34.4
Stroke, %	19.8	20.4
Hip fracture, %	15.3	12.8
Breast cancer, %	10.2	13.0
Endometrial cancer, %	0.0	0.0
Life expectancy, *y*	82.8	83.9

* Estimated lifetime probability of developing the condition (*see* Appendix 2).

Table C. Lifetime Probabilities of Selected Conditions for a 50-Year-Old White Woman Treated with Long-Term Hormone Replacement

Variable	Lifetime Probability*			
	No Treatment	Estrogen	E+P+E+P‡	
Coronary heart disease, %	46.1	34.2	34.4	39.0
Stroke, %	19.8	20.2	20.3	19.3
Hip fracture, %	15.3	12.7	12.8	12.0
Breast cancer, %	10.2	13.0	13.0	19.7
Endometrial cancer, %	2.6	19.7	2.6	2.6
Life expectancy, *y*	82.8	83.7	83.8	82.9

* Estimated lifetime probability of developing the condition (*see* Appendix 2). E + P = estrogen plus progestin.

† Assuming that the addition of a progestin to the estrogen regimen does not alter any of the relative risks for disease from estrogen therapy, except to prevent the increased risk due to endometrial cancer (relative risk for endometrial cancer estimated to be 1.0).

‡ Assuming that the addition of a progestin to the estrogen regimen provides only two thirds of the coronary heart disease risk reduction afforded by estrogen therapy (relative risk for coronary heart disease estimated to be 0.8) and relative risk for breast cancer in treated women is 2.0.

5.0 Prescribing Hormone Regimens

Three general hormone regimens are in common clinical use: 1) unopposed estrogen (such as conjugated equine estrogen, 0.625 mg daily or equivalent); 2) estrogen plus cyclic progestin (such as estrogen plus medroxyprogesterone acetate, 5 or 10 mg daily for 10 to 14 days per month or equivalent); and 3) estrogen plus continuous progestin (such as estrogen plus 2.5 to 5 mg of medroxyprogesterone acetate daily or equivalent).

Estrogen should be prescribed for daily use (171). Estrogen has been given intermittently (5 to 7 days per month off therapy) in the hope that this regimen would cause the endometrium to shed and protect against endometrial hyperplasia. Cyclic estrogen therapy does not produce endometrial shedding and rates of endometrial hyperplasia are similar in women treated with daily and cyclic estrogen (121). Both cyclic and continuous regimens of estrogen treatment have been shown to similarly increase risk for endometrial cancer (5, 7-10, 14, 173). Many women who are prescribed cyclic therapy report estrogen-deficiency symptoms such as hot flushes and insomnia during the period off treatment. Cyclic estrogen regimens are also more complex and difficult to follow than a daily regimen.

Cyclic estrogen plus progestin regimens are often constructed by prescribing estrogen on days 1 to 25 of the month, the added progestin during the last 10 to 14 days of estrogen use, and no hormones on days 25 to 31 of the month. When estrogen is prescribed daily, a cyclic estrogen plus progestin regimen can be achieved by adding a progestin on the first 10 to 14 days of the month. This cyclic regimen is easier for patients to follow, achieves good cycle control, and avoids estrogen-deficiency symptoms during the period off hormones. Continuous estrogen plus progestin regimens should prescribe estrogen daily and a progestin daily.

6.0 Overall Effect of Hormone Therapy

On the basis of incidence and mortality rates for endometrial cancer, breast cancer, CHD, hip fracture,

and stroke in untreated white women and summary relative-risk estimates as detailed above (Table A), we used modified lifetable methods to estimate the effect of use of various long-duration hormone regimens on life expectancy and lifetime probability of developing each disease (*see* Appendix 2).

6.1 Women Who Have Had a Hysterectomy

A 50-year-old woman who has had a hysterectomy cannot develop endometrial hyperplasia or cancer. When these women are treated with estrogen, lifetime probability of CHD is expected to decrease (34.4% compared with 46.2% untreated) as is the lifetime probability of hip fracture (12.8% compared with 15.3% untreated) (Table B). Primarily because of the protective effect on CHD, estrogen therapy is estimated to increase life expectancy by 1.1 years. Treated women may have a slightly increased lifetime probability of developing breast cancer (13% compared with 10.2% untreated) but would not have endometrial bleeding or require regular endometrial monitoring. There is no reason to treat women who have had a hysterectomy with progestins.

6.2 Women with a Uterus

In 50-year-old women with a uterus, estrogen treatment decreases the estimated lifetime probability of developing CHD (34.2% compared with 46.1% untreated) and hip fracture (12.7% compared with 15.3% untreated). Estrogen therapy is estimated to increase life expectancy by 0.9 years (Table C). The potential adverse effects of treatment with unopposed estrogen are an increased lifetime probability of breast cancer (13.0% compared with 10.2% untreated) and endometrial cancer (19.7% compared with 2.6% untreated). The increase in lifetime probability of breast and endometrial cancer is somewhat greater than might be anticipated because increased life expectancy allows a longer time at risk for these diseases. If endometrial screening is performed regularly, the risk for dying of endometrial cancer in women treated with estrogen should be small, but the risk of undergoing hysterectomy as treatment for estrogen- induced atypical endometrial hyperplasia or cancer is probably over 20% (30). Hysterectomy is generally well tolerated, but can result in infection, bleeding, major embolic events, and mortality in 0.1% to 2% of patients (174).

Unfortunately, the overall effect of treatment with estrogen plus progestin regimens is difficult to assess because data are inadequate to estimate relative risk among estrogen plus progestin users for several of the diseases under consideration. As noted above, the evidence is reasonably good that combination therapy does not increase risk for endometrial cancer or reduce the protective effect of estrogen alone for hip fracture. The effects of estrogen plus progestin regimens on CHD, stroke, and breast cancer risk, however, are not clear. To make rough estimates of the overall effect of combination hormone therapy, we evaluated two sets of circumstances that represent the likely limits of the effects of estrogen plus progestin therapy. As an optimistic estimate, we assumed that for users of estrogen plus a progestin, the relative risks for all diseases are the same as for users of unopposed estrogen except that there is no increased risk for endometrial cancer. As a pessimistic estimate, we assumed that about one third of the protective effect of unopposed estrogen on CHD is lost by the addition of a progestin (relative risk for CHD used in the model, 0.8) and that there is some additional increase in risk for breast cancer (relative risk for breast cancer used in the model, 2.0) (*see* Table A).

Table D. Lifetime Probabilities of Selected Conditions for a 50-Year-Old White Woman with Coronary Heart Disease Treated with Long-Term Hormone Replacement*

Variable	Lifetime Probability†			
	No Treatment	Estrogen	E+P‡	E+P§
Coronary heart disease, %	83.9	76.4	76.6	79.4
Stroke, %	11.2	13.2	13.3	11.8
Hip fracture,%	7.7	7.5	7.6	6.6
Breast cancer,%	7.9	10.7	10.7	15.9
Endometrial cancer,%	2.1	17.1	2.3	2.1
Life expectancy, *y*	76.0	78.1	78.2	76.9

* Relative risk of developing or dying of recurrent coronary heart disease was estimated as 5.0. E + P = estrogen plus progestin.

† Estimated lifetime probability of developing the condition (*see* Appendix 2).

‡ Assuming that the addition of a progestin to the estrogen regimen does not alter any of the relative risks for disease seen with estrogen therapy, except to prevent the increased risk due to endometrial cancer (relative risk for endometrial cancer estimated to be 1.0).

§ Assuming that the addition of a progestin to the estrogen regimen provides only two thirds of the coronary heart disease risk reduction afforded by estrogen therapy (relative risk for coronary heart disease estimated to be 0.8) and relative risk for breast cancer in treated women is 2.0.

Table E. Lifetime Probabilities of Selected Conditions for a 50-Year-Old White Woman at Risk for Coronary Heart Disease Treated with Long-Term Hormone Replacement*

Variable	Lifetime Probability†			
	No Treatment	Estrogen	E+P‡	E+P§
Coronary heart disease, %	71.2	59.6	59.8	64.4
Stroke,%	15.4	16.9	17.0	15.6
Hip fracture, %	11.3	10.2	10.2	9.2
Breast cancer, %	9.1	11.9	12.0	17.9
Endometrial cancer, %	2.4	18.6	2.5	2.4
Life expectancy, *y*	79.6	81.1	81.2	80.2

* Relative risk of developing or dying of coronary heart disease was estimated as 2.5, as for a woman who smokes or has hypertension or diabetes. E + P = estrogen plus progestin.

† Estimated lifetime probability of developing the condition (*see* Appendix 2).

‡ Assuming that the addition of a progestin to the estrogen regimen does not alter any of the relative risks for disease seen with estrogen therapy, except to prevent the increased risk due to endometrial cancer (relative risk for endometrial cancer estimated to be 1.0).

§ Assuming that the addition of a progestin to the estrogen regimen provides only two thirds of the coronary heart disease risk reduction afforded by estrogen therapy (relative risk for coronary heart disease estimated to be 0.8) and relative risk for breast cancer in treated women is 2.0.

Table F. Lifetime Probabilities of Selected Conditions for a 50-Year-Old White Woman at Risk for Hip Fracture Treated with Long-Term Hormone Replacement*

Variable	Lifetime Probability†			
	No Treatment	Estrogen	E+P‡	E+P§
Coronary heart disease, %	45.3	33.7	33.9	38.5
Stroke, %	19.3	19.8	20.0	19.0
Hip fracture, %	36.2	31.4	31.6	29.9
Breast cancer, %	10.1	12.9	12.9	19.5
Endometrial cancer, %	2.6	19.6	2.6	2.6
Life expectancy, *y*	82.4	83.4	83.5	82.6

* Relative risk for hip fracture was estimated as 3.0, as for a woman with low bone mineral density. E + P = estrogen plus progestin.

† Estimated lifetime probability of developing the condition (*See* Appendix 2).

‡ Assuming that the addition of a progestin to the estrogen regimen does not alter any of the relative risks for disease seen with estrogen therapy, except to prevent the increased risk due to endometrial cancer (relative risk for endometrial cancer estimated to be 1.0).

§ Assuming that the addition of a progestin to the estrogen regimen provides only two thirds of the coronary heart disease risk reduction afforded by estrogen therapy (relative risk for coronary heart disease estimated to be 0.8) and relative risk for breast cancer in treated women is 2.0.

If added progestins do not alter the effects of estrogen except to remove the increased risk for endometrial cancer due to unopposed estrogen therapy, then life expectancy is estimated to increase 1 year, lifetime probability of CHD and hip fracture would be substantially reduced, and endometrial cancer risk would not be increased (*see* Table C). The only risk associated with this regimen could be a small increase in lifetime probability of developing breast cancer (13.0% compared with 10.2% untreated). *However, if combination hormone regimens do not provide the full CHD benefit and cause an additional increase in risk for breast cancer,* then the overall benefit could be negligible. The estimated increase in life expectancy is only 0.1 years, and the estimated lifetime probability of breast cancer is increased substantially (19.7% compared with 10.2% untreated).

6.3 Women with or at Increased Risk for Coronary Heart Disease

A 50-year-old woman with CHD has a lifetime probability of recurrent CHD that is very high (83.9%) and a median life expectancy that is significantly shorter than for a woman who does not have CHD (76.0 compared with 82.8 years). Estrogen therapy would be expected to reduce the lifetime probability of recurrent CHD to 76.4% and to increase median life expectancy about 2.1 years (Table D). Similarly, in a woman who is at increased risk for CHD due to such factors as smoking, high blood pressure, or high blood cholesterol (relative risk for CHD assumed to be 2.5 in the presence of any one risk factor), the lifetime probability of CHD is high (71.2%), and the median life expectancy is shorter than for a woman who is not at increased risk for CHD (79.6 compared with 82.8 years). Treatment with estrogen is estimated to reduce the lifetime probability of CHD and to extend median life expectancy about 1.5 years (Table E). Because risk factors for CHD are probably multiplicative (175), risk for CHD among women who have two or more risk factors is very high, approaching the level in women who already have CHD. Accordingly, these women are predicted to benefit from estrogen therapy nearly as much as those with CHD. Accompanying these benefits, however, treated women might be subject to a small increase in risk for developing breast cancer and, if they have a uterus, a large increase in the probability of developing endometrial cancer (Tables D and E).

If added progestins do not alter the effects of estrogen except to remove the increased risk for endometrial cancer due to unopposed estrogen therapy, then women with CHD who are treated with combination therapy would be expected to have a substantially decreased lifetime probability of CHD and an increase of 2.2 years in life expectancy (*see* Table D). In women at increased risk for CHD, treatment with estrogen plus progestin would be expected to decrease lifetime probability of CHD and to extend life expectancy about 1.6 years (*see* Table E). As with estrogen therapy, however, these benefits are probably accompanied by a small increase in the lifetime probability of developing breast cancer. *Even if the addition of a progestin to estrogen therapy does not provide the full CHD benefit and causes an additional increase in risk for breast cancer,* treatment in women with CHD could reduce lifetime probability of recurrent CHD substantially and increase estimated life expectancy 0.9 years (*see* Table D). Similarly, life expectancy in women who are at increased risk for CHD would still be expected to increase 0.6 years (*see* Table E).

6.4 Women at Increased Risk for Hip Fracture

For a 50-year-old woman who is at increased risk for hip fracture due to such factors as low bone mineral density (relative risk for hip fracture assumed to be 3.0 for women with low bone density), the estimated lifetime probability of hip fracture is high (36.2%) and median life expectancy is shorter by 0.4 years compared with women who are not at increased risk for hip fracture. Treatment with estrogen is expected to decrease the lifetime probability of hip fracture to approximately 31.4% and extend life expectancy by 1 year. Lifetime probability of hip fracture does not decrease as much as expected because the additional year of life gained occurs, on the average, at an advanced age when the incidence of hip fracture is very high. A small increase in lifetime probability of breast cancer and, in those with a uterus, a large increase in lifetime probability of endometrial cancer would be expected among women treated with unopposed estrogen (Table F).

In women who are at increased risk for hip fracture, treatment with combination hormones is expected to result in a reduction in lifetime probability of hip fracture similar to that for unopposed estrogen. *If, however, the addition of a progestin provides only part of the CHD benefit of unopposed estrogen therapy and increases the risk for breast cancer twofold*, then the overall benefit would be small (estimated increase in life expectancy, 0.2 years), and the lifetime probability of breast cancer could be substantially increased (10.1% compared with 19.5% treated).

6.5 Women at Increased Risk for Breast Cancer

For a 50-year-old woman who is at increased risk for breast cancer due to such factors as a family history of breast cancer (relative risk for breast cancer assumed to be 2.0), the lifetime probability of breast cancer is high (19.3%), and median life expectancy is shorter by 0.5 years than in women who are not at increased risk for breast cancer. Treatment with estrogen is estimated to increase the lifetime probability of breast cancer from 19.3% to 24.1% and to increase lifetime probability of endometrial cancer substantially (Table G). Despite this increase in risk for cancer, life expectancy is still expected to increase 0.7 years due to reduced mortality from CHD and hip fracture.

If added progestins do not alter the effects of estrogen except to remove the increased risk for endometrial cancer due to unopposed estrogen therapy, then women at increased risk for breast cancer who are treated with combination therapy would be expected to have an increase in life expectancy of about 0.8 years. As with unopposed estrogen therapy, however, the lifetime probability of breast cancer may increase. *If the addition of a progestin to the estrogen regimen increases breast cancer risk as much as twofold*, then treating women at increased risk for breast cancer with combination hormones could result in a substantial increase in lifetime probability of breast cancer (35.1% compared with 19.3% untreated) and a slight *reduction* in life expectancy (*see* Table G).

6.6 Nonwhite Women

Most of the participants in studies of the effects of estrogen and of estrogen plus progestin were white. However, assuming that the relative risks for the diseases of interest are the same as in white women and using incidence and mortality data for black women (*see* Appendix 2), we also estimated the effect of hormone therapy in black women.

The lifetime probability of developing CHD in untreated black and white women is similar (46.5% in blacks compared with 46.1% in whites), but hip fracture (5.6% compared with 15.3% in whites), breast cancer (7.3% compared with 10.2% in whites), and endometrial cancer (1.5% compared with 2.6% in whites) are less common in black women and stroke is more common (26.0% compared with 19.8% in whites). Because CHD is the most common disease of both black and white women, the estimated risks and benefits of hormone therapy are similar in both groups. For example, black women who have had a hysterectomy are expected to have a reduction in lifetime probability of CHD and to gain 0.9 years of life expectancy if treated with estrogen. The expected benefit of hormone therapy in black women with CHD is almost identical to the benefit in white women with CHD: if treated with estrogen alone, a substantial reduction in lifetime probability of recurrent CHD and a gain in life expectancy of 1.9 years; if treated with estrogen plus a progestin, a substantial reduction in lifetime probability of CHD and a gain in life expectancy of 0.9 years, even if added progestin provides only two thirds of the benefit of estrogen therapy and increases the risk for breast cancer twofold.

We did not estimate the effects of hormone therapy for racial groups other than whites and blacks because reliable incidence and mortality data for the diseases of interest are not available. Because CHD is at least twice as common as any other disease among women of all races, however, the overall risks and benefits of hormone therapy are likely to be similar to those presented for white women.

7.0 Evaluation and Risk Stratification

Menopause signals the beginning of a period in life when risk for diseases such as CHD, stroke, cancer, and osteoporosis begins to increase. Accordingly, menopause is an appropriate time for a complete review of risk status and for counseling concerning risk factor reduction. Information concerning the risks and benefits of hormone replacement therapy should be part of this comprehensive risk assessment. Review of the known risk factors for breast cancer, CHD, and hip fracture may influence the decision to take hormones. Most of these risk factors can be determined by interview, but measurement of body weight, blood pressure, urine or serum glucose and cholesterol may be helpful. Occasionally, a woman will decide to take hormone therapy only if she knows that she is at increased risk for osteoporotic fractures. In that case, a single measurement of bone mineral density may be useful (176). The benefit of follow-up measurements of bone density to assess the effect of hormone therapy is, at best, uncertain.

8.0 Endometrial Cancer Screening

There are inadequate data to determine the best method and schedule of screening for endometrial can-

Table G. Lifetime Probabilities of Selected Conditions for a 50-Year-Old White Woman at Risk for Breast Cancer Treated with Long-Term Hormone Replacement*

Variable	Lifetime Probability†			
	No Treatment	Estrogen	E+P‡	E+P§
Coronary heart disease, %	44.9	33.1	33.3	37.1
Stroke, %	19.2	19.5	19.6	18.2
Hip fracture, %	14.8	12.2	12.3	11.2
Breast cancer, %	19.3	24.1	24.2	35.1
Endometrial cancer, %	2.5	19.3	2.6	2.5
Life expectancy, *y*	82.3	83.0	83.1	81.8

* Relative risk for developing or dying of breast cancer was estimated as 2.0, as for a woman with a mother or sister who has had breast cancer. E + P = estrogen plus progestin.

† Estimated lifetime probability of developing the condition (*see* Appendix 2).

‡ Assuming that the addition of a progestin to the estrogen regimen does not alter any of the relative risks for disease seen with estrogen therapy, except to prevent the increased risk due to endometrial cancer (relative risk for endometrial cancer estimated to be 1.0).

§ Assuming that the addition of a progestin to the estrogen regimen provides only two thirds of the coronary heart disease risk reduction afforded by estrogen therapy (relative risk for coronary heart disease estimated to be 0.8) and relative risk for breast cancer in treated women is 2.0.

Table H. Net Change in Life Expectancy for a 50-Year-Old White Woman Treated with Long-Term Hormone Replacement

Variable	Life Expectancy	Net Change in Life Expectancy		
		Estrogen	E+P*	E+P†
	← y →			
White woman, 50 years old				
No risk factors	82.8	+0.9	+1.0	+0.1
With hysterectomy	82.8	+1.1		
With history of coronary heart disease	76.0	+2.1	+2.2	+0.9
At risk for coronary heart disease	79.6	+1.5	+1.6	+0.6
At risk for breast cancer	82.3	+0.7	+0.8	−0.5
At risk for hip fracture	82.4	+1.0	+1.1	+0.2

* Assuming that the addition of a progestin to the estrogen regimen does not alter any of the relative risks for disease seen with estrogen therapy, except to prevent the increased risk due to endometrial cancer (relative risk for endometrial cancer estimated to be 1.0). E + P = estrogen plus progestin.

† Assuming that the addition of a progestin to the estrogen regimen provides only two thirds of the coronary heart disease risk reduction afforded by estrogen therapy (relative risk for coronary heart disease).

§ Assuming that the addition of a progestin to the estrogen regimen provides only two thirds of the coronary heart disease risk reduction afforded by estrogen therapy (relative risk for coronary heart disease estimated to be 0.8) and relative risk for breast cancer in treated women is 2.0.

cer in women taking hormones. The following recommendations are based on findings from endometrial screening in women not taking estrogen and on expert opinion (177). Women who plan to take unopposed estrogen should undergo pelvic examination and endometrial evaluation before beginning therapy to detect endometrial cancer or hyperplasia and have breast examination and mammography to detect breast cancer. Endometrial evaluation typically consists of histologic sampling accomplished by inserting a biopsy cannula through the cervical os into the endometrial cavity to obtain tissue. Such office-based endometrial biopsy is generally well tolerated and accurate (178-180). In some women, particularly older women with urogenital atrophy, it may be difficult to perform this procedure because of a small introitus or stenotic cervical os. These women may not be good candidates for unopposed estrogen therapy because regular endometrial tissue sampling is necessary. Tissue sampling can also be accomplished using dilation and curettage, but this procedure is more painful, invasive, and expensive, usually requiring sedation, anesthesia, and the support of an outpatient surgical suite.

Transvaginal ultrasonography has recently been used to evaluate the endometrium. Accumulating evidence indicates that transvaginal ultrasonography can accurately rule out endometrial hyperplasia or cancer in postmenopausal women. In all published reports to date, vaginal ultrasonography, using a definition of normal endometrium of 4 mm or less, has had a sensitivity of 100% and a negative predictive value of 100% (that is, no cases in which vaginal ultrasonography indicated normal endometrium but histologic examination showed atypical hyperplasia or endometrial cancer) (181-186). Thus, transvaginal ultrasonography may be a satisfactory screening test; endometrial tissue sampling could be performed only in women with endometrium thicker than 4 mm on the transvaginal ultrasound scan.

Women taking unopposed estrogen should be instructed to report any vaginal bleeding. If uterine bleeding occurs and no recent endometrial evaluation has been done, diagnostic endometrial evaluation should be performed. If bleeding does not occur, screening endometrial evaluation should be done—probably every year—but the optimal interval for screening endometrial evaluation has not been assessed. Clinical breast examination and mammogram should be performed yearly as in all women after 50 years of age.

Women who take combination estrogen plus progestin regimens do not require baseline or routine endometrial evaluation because the risk for endometrial cancer is not increased. Breast examination and mammography should be performed yearly. Withdrawal bleeding will occur in 30% to 80% of women taking cyclic estrogen plus progestin regimens. When the progestin is added to daily estrogen on days 1 to 12 of the month, endometrial evaluation is commonly performed to evaluate bleeding that begins at any time other than on days 5 to 15 of the month. Evaluation should also be performed if bleeding persists for more than 10 days.

About 30% to 50% of women who choose to use a continuous combined estrogen plus progestin regimen will develop erratic endometrial bleeding during the first 3 to 6 months of treatment. Women should be instructed to report any bleeding and endometrial evaluation should be performed if bleeding is prolonged (more than 10 days) or heavy (heavier than the woman's normal menses).

9.0 Helping a Woman Make an Informed Decision

The decision to take hormone therapy is complex. The overall effect is probably to increase life expectancy and to decrease the lifetime probability of CHD and hip fracture. Ideally, the woman should understand the likely changes in her risk for various diseases and the expected change in her life expectancy due to hormone treatment. She should know the common side effects of each regimen, the endometrial bleeding pattern to be expected, and the suggested type and frequency of endometrial monitoring.

A woman's assessment of the risks and benefits of hormone therapy is likely to depend on her risk status. For example, women with CHD are likely to place more value on prevention of recurrent CHD events than women at increased risk for breast cancer. Thus, each woman should participate in the decision concerning preventive therapy with hormones. Because of the complexity of the decision, information should be supplemented with printed material and adequate time allowed to make sure that a woman is fully informed.

10.0 Conclusions

Extensive and consistent evidence shows that estrogen therapy decreases risk for CHD and for hip fracture. The evidence is strong and consistent that long-

term estrogen therapy substantially increases endometrial cancer risk and weak evidence that long-term estrogen therapy is associated with a small increase in breast cancer risk. All of the data are observational, however, and are subject to bias. Only randomized trials can definitively establish the risks and benefits of estrogen therapy. The increase in endometrial cancer risk can probably be avoided by adding a progestin to the estrogen regimen for women who have a uterus. Unfortunately, the effects of combination regimens on risk for other diseases has not been adequately studied. Preliminary data indicate that there is some reason to worry that combination regimens could provide less benefit for CHD and cause higher risk for breast cancer than unopposed estrogen.

To provide information to women and their physicians without obscuring benefits or risks, we estimated changes in the lifetime probability of developing each major disease potentially affected by hormone use. To summarize the effect, we also estimated changes in life expectancy for women treated with hormones (Table H). Our estimates suggest that hormone therapy should probably be recommended for women who have had a hysterectomy and for those with CHD or at high risk for CHD. For other women, the best course of action is not clear.

In women who have had a hysterectomy and take estrogen, we estimate a substantial reduction in lifetime probability of CHD and hip fracture and an extension of life expectancy of 1.1 years. Therapy may be associated with a small increase in lifetime probability of breast cancer.

In women who have CHD, treatment with unopposed estrogen is expected to reduce the high lifetime probability of CHD and extend life an average of 2.1 years. Women at increased risk for heart disease, especially if two or more heart disease risk factors are present, should benefit similarly. However, in women who have not had a hysterectomy (whether or not they have heart disease), treatment with unopposed estrogen is likely to cause a large increase in lifetime probability of endometrial cancer. Endometrial cancer is rarely fatal among estrogen users and generally requires only hysterectomy as treatment. Nevertheless, the high probability of developing endometrial hyperplasia or cancer requiring hysterectomy and the requirement for periodic endometrial sampling will convince many women with a uterus who decide to take hormones to take combination therapy. Even if the added progestin removes up to a third of the CHD benefit of estrogen and increases breast cancer risk twofold, women with CHD will still benefit, reducing lifetime probability of CHD and increasing life expectancy about 0.9 years.

A woman at increased risk for hip fracture who chooses to take hormones should expect to reduce her lifetime probability of hip fracture. Her estimated gain in life expectancy (about 1 year) is largely due to reduced risk for CHD, however, and is similar to the gain in life expectancy for women not at increased risk for hip fracture. Women at increased risk for hip fracture may also have a greater risk for wrist and vertebral fractures, and hormone therapy also reduces these risks.

In women who are at increased risk for breast cancer, the decision regarding hormone therapy is difficult. Although the evidence is not consistent, long-term estrogen therapy may increase the risk for breast cancer slightly. When the lifetime probability of developing breast cancer is already high, the added risk caused by estrogen therapy may be unacceptable, despite the predicted increase in life expectancy of 0.7 years. There is some suggestion that combination regimens may increase breast cancer risk more than unopposed estrogen therapy. If this is true, treatment with combination hormones could result in an actual *decrease* in life expectancy for women at increased risk for breast cancer. Given this uncertainty, many women at increased risk for breast cancer may choose not to take hormones as preventive therapy. Estrogen therapy has been shown to promote growth of malignant breast tumors in animals. Because breast cancer may recur many years after primary therapy, estrogen is generally not prescribed for women who have had breast cancer.

For women with a uterus and no particular risk factors, the best course of action is not clear. Some women may choose to take unopposed estrogen because the effects of combination therapy are uncertain. Estrogen therapy is estimated to reduce lifetime probability of CHD and hip fracture and extend life expectancy about 0.9 years but is likely to be associated with a large increase in lifetime probability of endometrial cancer and may be associated with a small increase in breast cancer risk. For most women and their physicians, the expected large increase in risk for endometrial cancer and the need for regular endometrial monitoring will probably make treatment with unopposed estrogen unacceptable. Adding a progestin to the estrogen therapy eliminates the increased risk for endometrial cancer associated with unopposed estrogen use, but the estimation of the effects of combination therapy on other diseases contains considerable uncertainty. Using optimistic estimates, lifetime probabilities for CHD and hip fracture are likely to be substantially reduced and life expectancy extended 1 year in women treated with estrogen plus a progestin. Pessimistic estimates suggest that the overall benefit may be negligible and accompanied by a substantial increase in lifetime risk for breast cancer.

The risks and benefits of hormone therapy are probably similar in white and nonwhite women. It has been thought that hormone therapy need not be considered for black women because their risk for hip fracture is less than in white women. Because CHD is equally common in white and nonwhite women, hormone therapy should be considered in all women who have had a hysterectomy and in those with CHD or who are at high risk for CHD.

11.0 Discussion

We have evaluated the risks and benefits of hormone therapy in asymptomatic postmenopausal women who are considering hormone use to prevent disease and prolong life. We did not include the effect of hormone therapy on conditions that do not significantly affect mortality such as wrist fracture, vertebral fracture, and gallbladder disease. Perhaps the greatest weakness of our assessment is that we did not evaluate the effect of therapy on quality of life, which may be the most im-

portant consideration for many women. Potential benefits of hormone therapy such as prevention of kyphosis, preservation of urinary and sexual function, prevention of skin aging, and improved sense of well-being might be more important to some women than preventing disease and death. Similarly, drawbacks to hormone therapy such as side effects, vaginal bleeding, the need to take daily medication, the need for regular physician visits and endometrial monitoring, and the fear of cancer might outweigh the perceived benefits. In general, hormone therapy is expected to reduce the risk for CHD and hip fracture and to extend life expectancy, but the impact of these changes on quality of life is not clear. Preventing a hip fracture at age 79 (the mean age at which fractures occur) will improve quality of life if it allows a woman to remain active and independent. Preventing a heart attack at age 74, however (the mean age at which heart attack occurs), might not improve quality of life if a woman is institutionalized with medical problems and chronic disability.

The predicted extension of life expectancy due to hormone therapy is similar to or greater than that expected for other preventive strategies. The predicted extension in life expectancy for women with a hysterectomy who take long-duration estrogen is 1.1 years and for women with heart disease is about 2.1 years. For comparison, the estimated gain in life expectancy for a 35-year-old woman treated for mild hypertension is 0.9 years and for moderate hypertension is 1.7 years (187).

Many women will not fit into one of the risk groups that we evaluated. In these cases, changes in lifetime probabilities and life expectancy can be approximated based on the data that we have presented in Tables B through H. A women who has had a hysterectomy *and* has heart disease, for example, will benefit more than a woman with a uterus who has heart disease. A woman at increased risk for breast cancer who has heart disease will benefit somewhat less than a woman with heart disease who is not at increased risk for breast cancer.

In the absence of definitive evidence, we used the "best" estimate of the change in risk for various diseases associated with hormone therapy. The most important estimates are the relative risks for CHD (the most important potential benefit) and breast cancer (the most important potential risk) associated with hormone therapy. Our estimate of a relative risk of 0.65 for CHD among women who use long-term estrogen does not differ materially from other summary estimates by Bush of 0.55 (74) or Stampfer and colleagues of 0.58 (75). Repeating the analyses using a relative risk of 0.55 for heart disease increases the benefit of hormone treatment somewhat, but does not substantially alter our findings. Our estimate of a relative risk of 1.25 for breast cancer among women who use long-term estrogen is very similar to a summary estimate of 1.3 by Steinberg and colleagues (42). Because data concerning the effect on CHD and breast cancer risk of adding a progestin to the estrogen regimen are limited, we evaluated a range of reasonable assumptions.

Because both CHD and breast cancer are common and deadly, the effect on the risk-benefit analysis of varying these assumption is substantial. Based on the "optimistic" assumption that progestins provide all of the benefit of estrogens and prevent an increase in endometrial cancer risk, most postmenopausal women would benefit from hormone therapy, reducing lifetime probability of CHD and hip fracture and extending life expectancy a full year. Using the "pessimistic" assumption that combination hormones provide only two thirds of the CHD benefit of estrogen *and* increase breast cancer risk twofold, the benefit is negligible, and the risk for breast cancer may increase substantially. This uncertainty clearly identifies the need for additional studies of the effect of long-duration combination hormone therapy. Evaluation of the risks and benefits of therapy should be reviewed as new evidence emerges.

We considered the relative benefits of three common hormone regimens: unopposed estrogen, estrogen plus cyclic progestin, and estrogen plus continuous progestin. However, many estrogens and progestins are available, and regimens for combining progestin with estrogen are evolving. Use of different types or regimens of hormone therapy could affect our conclusions, as could new data on the effects of estrogen plus progestin regimens on risk for CHD, stroke, and breast cancer.

A woman must be fully informed of the risks and benefits of hormone therapy and play an important role in deciding whether to take hormones and which regimen to use. A woman's risk factors for CHD, hip fracture, and breast cancer and whether she has had a hysterectomy may affect the decision. For many women, however, the value placed on prevention of CHD compared with the desire to avoid cancer will probably determine whether she takes hormones as preventive therapy.

Appendix 1. Calculation of Summary Relative Risks

Review of the Literature

We attempted to retrieve all English-language studies of the association of postmenopausal hormone therapy and endometrial cancer (*see* Table 1), breast cancer (*see* Table 2), coronary heart disease (*see* Table 3), hip fracture (*see* Table 4), and stroke (*see* Table 5) that were published after 1970. We conducted computerized literature searches using the MEDLINE data base, manual literature searches by reviewing reference lists in relevant papers, and consultations with colleagues and experts.

This search identified 51 published articles that provided risk estimates for endometrial cancer (5-18, 20, 22, 23, 25, 28-32, 37, 62-65, 80, 173, 188-207), 55 that provided risk estimates for breast cancer (31, 37, 43-59, 61, 62, 65, 68, 69, 80, 132, 197-204, 208-227), 37 that provided risk estimates for CHD (61, 63, 64, 70-73, 76-85, 96, 101, 113, 114, 117, 134, 197, 204, 221, 228-241), 11 that provided risk estimates for hip fracture (102, 117, 124, 125, 242-248), and 20 that provided risk estimates for stroke (61, 63, 73, 76-78, 80, 85, 112, 114, 116, 117, 134, 197, 204, 221, 234, 249-252), comparing women who used postmenopausal hormone therapy with nonusers.

If results from a single study were reported in multi-

ple publications, we included in our literature tables (*see* Tables 1 to 5) only the one that provided data on the most cases or was most recently published. Publications excluded for this reason include: 10 endometrial cancer studies (37, 197, 199-203, 205-207); 16 breast cancer studies (31, 37, 199-203, 208, 210, 213, 214, 217, 220, 221, 223, 226); 8 CHD studies (72, 134, 197, 221, 232, 236, 239, 253); no hip fracture studies; and 4 stroke studies (80, 197, 221, 251). The remaining publications were included in Tables 1 to 5.

Inclusion and Exclusion Criteria for Meta-Analysis

From the references listed in Tables 1 to 5, we abstracted estimates of relative risk for ever-use of postmenopausal hormones (risk in ever-users compared with risk in never users). When possible, we also extracted the relative risk for long-term hormone use (risk in long-term users compared with nonusers) and use of standard-dose estrogen (risk in users of 0.625 mg of conjugated estrogen or equivalent daily compared with nonusers). When necessary, we excluded data from premenopausal women and combined data for various control groups (such as hospital and community) or subgroups of women (such as those with natural menopausal or surgically menopausal).

We excluded studies in Tables 1 to 5 from inclusion in the meta-analyses for the following reasons:

1. No confidence intervals were provided, and we were unable to calculate confidence intervals using the data in the publication. References excluded for this reason include one endometrial cancer study (8); one breast cancer study (209); and no studies of CHD, hip fracture, or stroke.

2. The study used inappropriate participants, such as premenopausal women or women with specific diseases. References excluded for this reason include two endometrial cancer studies (80, 195); two breast cancer studies (80, 254); three CHD studies (71, 117, 233); one hip fracture study (117); and one stroke study (117).

3. The study used an inappropriate comparison group, such as general population disease rates. References excluded for this reason include five endometrial cancer studies (62, 63, 196, 198, 204); six breast cancer studies (61-63, 196, 198, 204); five CHD studies (61, 63, 101, 204, 234); no hip fracture studies; and four stroke studies (61, 63, 204, 234).

4. The study reported only combined end points (such as coronary heart disease and stroke or hip and forearm fracture). References excluded for this reason include no endometrial cancer or breast cancer studies; one CHD study (114); two hip fracture studies (102, 124); and one stroke study (114).

Calculation of Pooled Relative Risks

The estimated relative risk from each study was treated as one stratum. To calculate a summary estimate of the relative risk and variance of the overall effect, estimates from each stratum were combined. The summary relative risk was estimated by assigning a weight for the relative risk from each study that was equal to the inverse of the variance of the estimated relative risk. Thus, the weight for each relative risk was proportional to the precision of the results (189), with large studies carrying more weight than small studies. This method of pooling data assumes that the effect of hormone therapy on disease incidence and mortality is uniform in all of the studies included. For each disease, a chi-square test of heterogeneity was performed to determine if the data on long-term estrogen use were compatible with this assumption. Evidence of significant heterogeneity was present for the stroke data.

Using these methods, we calculated summary relative risks for ever-use of estrogen, and where possible, ever-use of combined estrogen and progestin and long-term use of estrogen.

Appendix 2. Estimation of Lifetime Probability of Developing Disease and Life Expectancy

Sources of Data

Mortality Data

We used age- and race-specific mortality rates for coronary heart disease (ICD-9 codes 410 to 414) and cerebrovascular disease (ICD-9 codes 430 to 438) among white and black women from the 1987 *Vital Statistics of the United States* (255). For breast and endometrial cancer, we used age- and race-specific mortality rates from the Surveillance, Epidemiology and End Results program (256). No adequate population-based mortality rates exist for hip fracture. Approximately 5% to 20% more patients with hip fractures die within the first year after the fracture than would be expected on the basis of their age and sex (257-259). This excess mortality rate increases with age. On the basis of recent reviews of hip fracture and subsequent mortality (259-261), we estimated that the excess mortality for hip fractures within 1 year of fracture was 5.4% for women under 75 years, 8.0% for women from age 75 to 84 years, and 13.2% for women 85 years or older.

Incidence Data

Age- and race-specific incidence rates for breast and endometrial cancer are from the Surveillance, Epidemiology and End Results Program (256). Age-specific hip fracture rates for white women were estimated using hospital discharge data from the National Hospital Discharge Survey (262). Hip fracture incidence rates for black women were estimated using hospital discharge data from non-federal hospitals in the District of Columbia metropolitan area (262). To estimate the age- and race-specific incidence rates for coronary heart disease and cerebrovascular disease among white and black women, we used age-specific mortality rates for coronary heart disease (ICD-9 codes 410 to 414) and cerebrovascular disease (ICD-9 codes 430 to 438) from the 1987 *Vital Statistics of the United States* (255) and applied age-specific case-fatality rates among white women from the Framingham Heart Study (263).

Calculation of Lifetime Probability of Developing Disease and Life Expectancy

The lifetime probability of a condition is defined as the probability of developing that condition before

death. Using adapted life table methods (264, 265), we calculated the lifetime probability of developing coronary heart disease, stroke, breast cancer, endometrial cancer, and hip fracture. We began our estimates at age 50, about the mean age of menopause, and assumed that all women would die in the interval of 90 to 94 years. We stopped the calculations at age 94 because no reliable data are available about the incidence of coronary heart disease, stroke, breast cancer, endometrial cancer, hip fractures, or mortality rates after age 94. This method tends to underestimate lifetime probabilities, but this effect is small because only a very small proportion of women are alive after age 94.

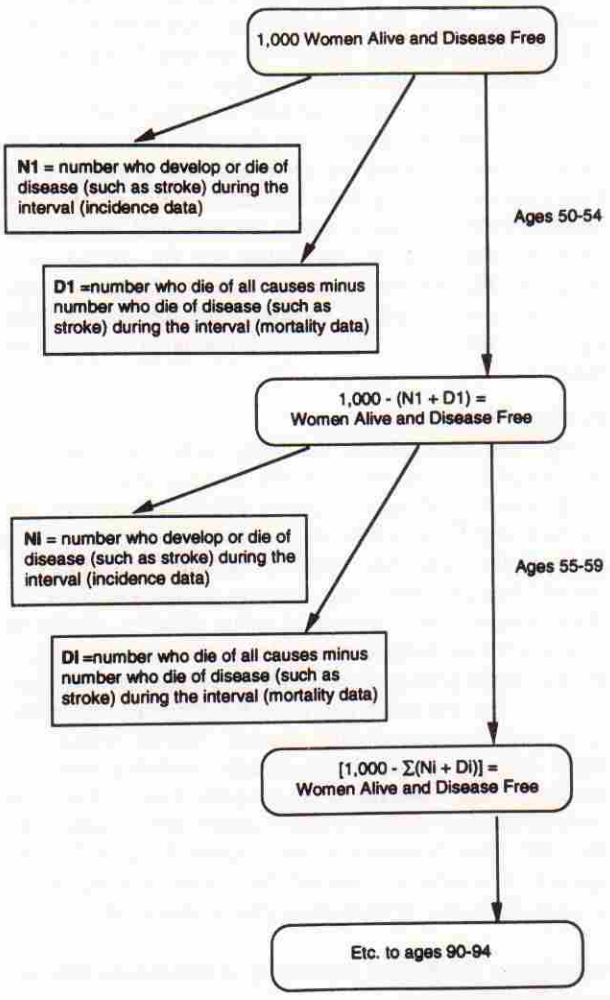
The calculation is outlined in Appendix Figure 1. We start with a model cohort of 1000 women who are 50 years old. We then calculate the number expected to develop or die of the disease in the first 5-year interval (N_1) (based on race- and age-specific incidence and mortality rates for the disease of interest) and the total number expected to die of all causes other than the disease of interest (D_1) in the interval (based on race- and age-specific, all-cause mortality rates). Thus the number surviving to age 55 years free of disease is $1000 - N_1 < 23 > D_1$. The process is then repeated to age 94. Lifetime probability of developing a specific disease is then estimated as the total number who develop disease ($N_1 + N_2 \ldots N_i$) divided by 1000.

The median age of developing disease is defined as the age at which half of the cases of disease occurred. Life expectancy is defined as the age at which half of the imaginary cohort of women died.

To calculate the lifetime probability of developing specific diseases and life expectancy among women when treated with hormone regimens, we used the same lifetable methods but multiplied the population disease incidence and mortality rates by the summary relative risk from the meta-analysis. For example, to calculate the lifetime probability of CHD among women treated with estrogen, we multiplied the incidence of CHD and the mortality rate from CHD in each 5-year age and race interval by 0.65 (the summary relative-risk estimate from the meta-analysis for the effect of estrogen on CHD risk). We multiplied both the incidence and mortality by the same relative risk for each disease except for endometrial cancer, where we used a relative risk for developing disease of 8.22 and a relative risk for dying of disease of 3.00 (*see* section 3.1).

We estimated the lifetime probability of developing specific diseases and life expectancy among women at risk for various diseases by multiplying baseline disease incidence and mortality rates by the estimated relative risk for women in a specific group. For example, to calculate the lifetime probability of recurrent CHD events and life expectancy among women with CHD, we used population-based estimates of the incidence of CHD and the mortality rate from CHD in each 5-year age and race interval and multiplied by 5 (the estimated relative risk for recurrent CHD events among women with CHD). Population-based disease rates are an average of rates in women with and without risk factors for disease. Using these rates as baseline estimates, rather than disease rates in women without risk factors (which are unavailable), is likely to underestimate both the risks and benefits of hormone therapy.

Finally, we calculated the lifetime probability of developing specific disease and life expectancy among these at risk when treated with hormones just as for women not at risk for disease.



Appendix Figure 1. Schema of a hypothetical cohort of 1000 women. Calculation of the number of women in this cohort who will develop or die of the condition of interest.

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