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CLINICAL PERSPECTIVES

Benefits and Risks of Menopausal Estrogen and/or Progestin Hormone Use[1,2]

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Current evidence is reviewed here on risks and benefits of estrogen and progestin use by peri- and postmenopausal women in relation to the following conditions: endometrial cancer, breast cancer, osteoporosis, and coronary artery disease (CAD). On balance, estrogen therapy appears to be beneficial for menopausal women, as it probably reduces the risks of CAD and osteoporosis, two of the major causes of mortality and morbidity. Although unopposed estrogen therapy increases the risk of endometrial cancer, that cancer is relatively rare and is not fatal in the vast majority of cases associated with estrogen use. Definitive conclusions about the relation of menopausal estrogens to breast cancer cannot be drawn due to inconsistent evidence to date. Although evidence from randomized controlled trials is lacking, biochemical and clinical evidence suggest that progestin supplementation is associated with a reduction in endometrial cancer risk in women taking menopausal estrogens. Progestin supplementation also may augment the beneficial effects of estrogens in providing protection against osteoporosis, although this effect is not yet well established. There is little direct evidence bearing on the relation of menopausal progestins to breast cancer. Although studies of CAD per se are lacking at present, progestins probably unfavorably alter lipoprotein profiles, thereby increasing a user's risk of CAD. Given the relatively high incidence and mortality of CAD in postmenopausal women, any negative effects on CAD risk could potentially counterbalance beneficial effects on other causes. We conclude that estrogen replacement therapy is of potential benefit to postmenopausal women, but that the question of progestin supplementation requires further study, particularly for CAD risk.

INTRODUCTION

Considerable controversy surrounds the use of estrogens and progestins by peri- and postmenopausal women. Some risks and some benefits of menopausal

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hormone use have been clearly established. However, the risk–benefit equation cannot be formulated definitively at present owing to inadequate information in several key areas. This article reviews current evidence, prefaced by a brief discussion of recent trends in the prevalence of menopausal hormone use.

Trends in Prevalence of Menopausal Hormone Use

In the United States there was a dramatic increase in dispensed retail prescriptions for noncontraceptive estrogens between the mid-1960s and the early 1970s (90% of noncontraceptive estrogens in 1983 were used by women, and 56% of the associated diagnoses in women were related to aging, i.e., menopausal symptoms, senile vaginitis, and osteoporosis (66)). After reports of possible association with endometrial carcinoma (124, 154), sales of noncontraceptive estrogens dropped in 1976 by almost 30%, with the greatest decline in the high-dose estrogen products. This downward trend continued until 1980. Since then, there have been annual increments in noncontraceptive estrogen prescriptions (66). Estrogen replacement therapy at menopause most commonly consists of conjugated natural estrogens (unlike the synthetic formulations in oral contraceptives). Recently, transdermal estrogen (estradiol) has been prescribed for postmenopausal women (75); however, published reports of its safety and efficacy are too preliminary and will not be considered in this review.

Trends in concomitant prescriptions of Premarin (the conjugated estrogen most frequently prescribed for menopausal women) with Provera (the most frequently prescribed progestin) showed steady increases between 1980 and 1983 (66). Since 1983, the upward trends have continued, with progestin supplementation of estrogen prescriptions becoming increasingly more common (Dianne L. Kennedy, FDA, personal communication). Progestins (or progestogens) include the natural hormone (progesterone) and synthetic derivatives. Menopausal women in the United States receive the synthetic derivatives. Although there are a great many synthetic formulations with widely varying therapeutic effects, the most commonly prescribed forms are the 19-nortestosterone derivatives (e.g., norethindrone) and the hydroxyprogesterone derivatives (e.g., medroxyprogesterone acetate). In the United States in 1983, of all oral noncontraceptive progestin prescriptions, about 11% were for norethindrone and 89% for medroxyprogesterone (including Provera). This distribution may not exactly reflect the experience of menopausal women because progestins are given for a number of conditions other than menopausal symptoms.

ESTROGENS

Estrogen replacement therapy has long been known to protect against the occurrence of such menopausal symptoms as hot flashes and vaginal dryness and itching. The greatest concern about risks associated with menopausal estrogens has focused on endometrial and breast cancers.

Endometrial Cancer: Increased Risk

For 1987, the American Cancer Society has estimated that there were 2,900 deaths and 35,000 new cases of endometrial cancer in the United States (3). The

disease generally presents with vaginal bleeding, is usually diagnosed at an early stage, and has a favorable prognosis (i.e., 92% 5-year relative survival among white women with Stage I disease and 84% for all stages combined) (95). The average annual age-adjusted incidence rate was higher in 1978–1981 for white (25.1 per 100,000 population) than for black (13.4 per 100,000) (139) women.

The magnitude of increase in reported endometrial cancer incidence rates in the late 1960s and early 1970s suggested that a change might have occurred in the nature or frequency of exposure to a causative environmental agent (145). The inference about the likely determinant for this incidence pattern was revealed in 1975 with the publication of two case–control studies showing four- to sevenfold relative risk estimates for the association of estrogen replacement therapy with endometrial cancer (124, 154). These reports were followed by a succession of epidemiologic studies that demonstrated elevated relative risks and dose–response relationships associated with estrogen use (Table 1).

Following the declining trend in estrogen prescriptions during the late 1970s, endometrial cancer incidence rates diminished (7, 143). Although the incidence of endometrial cancer increased in the early 1970s, the concurrent age-adjusted mortality rates remained relatively stable between 1973 and 1981 (95). The stable mortality in the context of rising incidence may be attributed to a general trend toward improving survival in the population and to the fact that a significant proportion of cases among estrogen users were early-stage lesions (26) (Table 2).

Duration of estrogen use and cumulative dose are major predictors of endometrial cancer risk (6, 41, 57, 58, 65, 85, 90, 120, 121, 129, 146). One year of use is probably the minimum exposure associated with increased risk (90, 129), although some studies have reported an increase in risk only with 3 or more years of use.

Following cessation of use, the period of time after cessation of use required before elevated risks approach those of the nonuser has not been determined precisely. Some studies have described short time intervals of 6 months to 2 years (57, 85), whereas one multi-hospital case–control study reported persistently increased risks up to 10 years after cessation of use (121). The data comparing trends of estrogen prescription volume with endometrial cancer incidence rates during the late 1970s are more consistent with the evidence for a relatively short time interval between cessation and decline in endometrial cancer risk (7).

These epidemiologic data have resulted in important changes in patient management (4). First, lower doses of estrogen, such as the 0.625-mg daily dosage, are being prescribed, and cyclic therapy is generally recommended, with 1 week of each 4-week cycle to be estrogen-free. Second, progestins are frequently being added during the last 10 days of the estrogen cycle to counteract the proliferative effects of estrogens on the endometrium (see below for the benefits of progestins). Third, physicians are more apt to wean women off hormone therapy after some months or a few years of use to avoid the elevated risks that occur with increasing duration of use. The effort to minimize duration of use runs contrary to the optimal regimen for the prevention of osteoporosis and associated fractures. The potential for causing endometrial cancer may be diminished through careful administration of the minimal therapeutically effective dose of estrogen, in conjunction with cyclical progestins (see below).

TABLE 1

CASE–CONTROL STUDIES SHOWING ASSOCIATION BETWEEN ESTROGEN USE AND ENDOMETRIAL CANCER

Author (reference)	Location of study	Inclusive years of diagnosis for selection of cases	Selection of controls	Percentage of estrogen use		Duration of estrogen use (years)—Relative risk
				Cases	Controls	
Smith *et al.* (124)	Seattle	1960–1972	Gynecologic cancers	48 (Any estrogen, 6 months or longer)	17	Overall . . . 4.5 Risk ratio varies with type of gynecologic cancer control; vulva (3.8), ovary (8.6), cervix (13.8)
Ziel and Finkle (154)	Los Angeles	1940–1974	Community	57 (Conjugated estrogens any duration)	15	Overall . . . 7.6 1–5 . . . 5.6 5–6 . . . 7.2 7+ . . . 8.8
Mack *et al.* (85)	Los Angeles	1971–1975	Community	89 (All estrogens any duration)	50	Overall . . . 8.0 <1 . . . 2.8 1–4 . . . 4.5 7+ . . . 8.8
McDonald *et al.* (90)	Rochester (MN)	1945–1974	Mayo Clinic admissions	11 (Conjugated estrogens, 6 months or longer)	3	Overall . . . 4.9 0.5–3 . . . 2.0 3+ . . . 7.9
Gray *et al.* (41)	Louisville	1947–1976	Patients with hysterectomies in private practice	16 (Conjugated estrogens, 3 months or longer)	6	Overall . . . 3.1 <4 . . . 1.2 5–9 . . . 4.1 10+ . . . 11.5
Antunes *et al.* (6)	Baltimore	1973–1977	Hospital, gynecologic and nongynecologic	19 (Any product containing estrogen alone, any duration)	5	Overall . . . 2.4 to 5.5 <1 . . . 2.2 1–5 . . . 2.9 ≥5 . . . 15.0
Hulka *et al.* (56)	Chapel Hill	1970–1976	(1) Hospital, gynecologic admissions (2) Community—52 counties in North Carolina	33 (All estrogens, any duration)	23–27	Overall . . . 1.4 to 1.8 <3.5 . . . 0.7 to 0.8 ≥3.5 . . . 3.6 to 4.1

Source: Ref. 117.

TABLE 2
AGE-ADJUSTED INCIDENCE, MORTALITY, AND SURVIVAL FOR UTERINE CORPUS CANCER, WHITE FEMALES, UNITED STATES

Year	Incidence/ 100,000	Year	Mortality/ 100,000	Year	5-Year relative survival
1969	22.6				
1971	24.6				
1973	29.0	1973–1977	1.9	1970–1973	81%
1975	32.4				
1977	28.5				
1978–1981	25.1	1978–1981	2.1	1974–1979	87%

Sources: SEER Cancer Incidence and Mortality in the United States, 1973–1981, and "Cancer Rates and Risks," 3rd ed. National Institutes of Health, Bethesda, MD, 1985.

Breast Cancer: Inconsistent Evidence

In Western Europe and North America, breast cancer represents the most frequent cancer in women, excluding the incidence of nonmelanoma skin cancers. In these countries, breast cancer accounts for about 4% of all deaths, 20% of all cancer deaths, and 25% of all cancer cases in women. For 1987, the American Cancer Society estimated that there were 130,000 new cases and 40,900 deaths from breast cancer (3).

As the evidence for a causal relationship of noncontraceptive estrogen replacement therapy with endometrial cancer became apparent, there was increased interest in determining a potentially similar relationship of estrogens and breast cancer. The assumption seemed reasonable because of estrogen receptor activity and estrogen dependency in both target organs and because both cancers seem estrogen dependent. Moreover, endometrial and breast cancers share some hormonally related risk factors (e.g., nulliparity).

The case–control studies of breast cancer published before 1980 that had specifically considered estrogen use were uniformly negative (55). Two cohort studies suggested an association; one, in particular, showed an increased risk among exposed women only after 10 years of follow-up (51).

Since 1980, several case–control studies have been reported (9, 48, 50, 56, 62, 64, 115, 151), and at least one prospective study (37) has appeared in various versions in several journals. That study purported to show a reduced breast cancer risk among estrogen-exposed women compared with those not exposed.

Ten case–control studies published since 1980 are summarized in Table 3. Some were population-based, while others relied on hospitalized control groups. Many geographic areas within the United States and elsewhere were represented. Most provided analyses separately for pre- and postmenopausal women and for natural versus surgical menopause; one was limited to women under age 55 (150, 151). Most authors chose to examine data separately for women who had had bilateral oophorectomy from those who had undergone a natural menopause, which is appropriate in that the two groups differ with respect to their risk of breast cancer and endogenous estrogen levels. The accumulated knowledge from these studies is inconsistent and controversial. Hoover *et al.* (50) and La Vecchia *et al.* (76)

TABLE 3

CASE–CONTROL STUDIES OF REPLACEMENT ESTROGENS AND BREAST CANCER RISK AMONG POSTMENOPAUSAL WOMEN, 1980–1985

Author (study site)	Source and number		Relative risk from ever use of menopausal estrogens	95% Confidence interval	Comments
	Cases	Controls			
Ross *et al.* (115)	Retirement community		Overall 1.1	0.8–1.9	Increased risk with total
(Los Angeles)	131	262	Ovaries removed 0.8	0.5–3.5	milligram dose; no data on
			Intact 1.4	0.7–2.4	duration of use
Brinton *et al.* (9)	BCDDP screening program		Overall 1.2	1.0–1.5	Increased risk with
(28 geographic areas)	881	863	Ovaries removed 1.5	0.9–2.8	increased dose; no
			Intact 1.2	0.9–1.5	duration effect on risk
Hoover *et al.* (50)	Kaiser Foundation		Overall 1.4	1.0–2.0	Increased risk with
(Portland)	Health Plan		Ovaries removed 1.5	0.3–6.6	increased number of
	324	549	Intact 1.3	0.8–2.1	prescriptions and
	(Pre- and post-menopausal)				increased daily dose
Kelsey *et al.* (64)	Three hospitals		Ovaries removed 0.9	0.5–1.5	No effect of increased
(Connecticut)	332	1353	Intact 0.9	0.6–1.2	milligram months of use
	(Age 45+, not all postmenopausal)				on risk
Hulka *et al.* (56)	Three hospitals		Ovaries removed 1.3, 1.2	not significant $P \leq 0.05$	Increased risk with
(North Carolina)	199	451 Community 852	Intact 1.3, 1.2		injectable estrogens, no dose or duration effects on risk

Hiatt *et al.* (48) (Northern California)	Kaiser Foundation Health Plan 119 (All with bilateral oophorectomy)	119	Ovaries removed 0.7	0.3–1.6	Increased risk with increased number of prescriptions; no duration effect on risk
Wingo *et al.* (151) (8 geographic areas)	Population based 705 (Age <55)	1027	Overall 1.0 Ovaries removed 1.1 Intact 0.6	0.8–1.3 0.8–1.5 0.4–1.2	No dose, duration, or subgroup effect on risk
Kaufman *et al.* (62) (Canada)	Multiple hospitals 925	1127	Overall 0.9	0.7–1.1	No dose, duration, or subgroup effect on risk
La Vecchia *et al.* (76) (Milan, Italy)	1,108 Hospital	1,281	Total study group 1.9	1.4–2.8	Increased risk with duration of use among women with natural menopause, but not among those with surgical menopause; no interaction within high-risk subgroups
Wingo *et al.* (150) (8 geographic areas)	1369 Population tumor registry (Age <55)	1645 Community	Total study group 1.0 Ovaries removed 1.3 Natural menopause 0.8	0.9–1.2 0.9–1.9 0.6–1.1	Increased risk by dose and duration of use among women with both ovaries removed, and particularly, within subgroups, 50–54 years of age at diagnosis, or with first-degree relative with breast cancer
Brinton *et al.* (10) (28 geographic areas)	BCDDP screening program (expansion of Ref. 9) 1,960	2,258	Overall 1.0 Ovaries removed 1.14 Intact 1.01	0.9–1.2 0.8–1.2	Increased risk with increased duration; no dose–response effect for Premarin

noted an increased risk for breast cancer associated with estrogen use, whereas Kelsey (64), Hulka (56), Hiatt (48), Wingo (150, 151), Kaufman (62), and their respective coauthors reported no elevation in risk. Ross *et al.* (115) showed an increased breast cancer risk for women who had undergone a natural menopause. Brinton *et al.* originally suggested that increased risk occurred primarily among those whose menopause occurred as a result of bilateral oophorectomy (9), but based on a later analysis (10) of their expanded case–control data, the authors found no significant elevations in risk associated with ever use of menopausal hormones in any of the menopause groups studied (natural, ovaries retained, and ovaries removed). As noted below, however, they did find an elevation in risk associated with long-term use.

In most studies, protracted estrogen use did not show the risk enhancement that was observed with endometrial cancer. None of these studies summarized in Table 3 reported a significant duration effect, with the exception of the expanded analysis of Brinton *et al.* (10) which showed an increase in risk with use duration across the menopausal groups studied; use of menopausal estrogens for 20 or more years was associated with a 50% increase in risk. The suggestion of a dose effect appears, however, in several of the studies. Ross *et al.* (115) demonstrated increasing risk with increasing doses. Hoover *et al.* (50) and Hiatt *et al.* (48), whose data on estrogen use were based on medical records, showed increased relative risks with increased number of prescriptions, a proxy indicator for intensity of estrogen use. Hulka *et al.* (56) found an increased risk with injectable estrogen; parenteral administration delivers high circulating levels of biologically active doses to the target organs, because it bypasses the enterohepatic circulation and hepatic deactivation. Brinton *et al.* reported an increased risk of breast cancer with increasing estrogen dose in their original analysis (9), but this was not confirmed in their expanded analysis (10). Kelsey *et al.* (64) found no association of breast cancer and milligram-months of estrogen use; nor was an association demonstrated in the Wingo *et al.* (151) and Kaufman *et al.* (62) studies that assessed estrogen dosages. The finding of a dose–response relationship in some studies is noteworthy and would be supportive of a causal association, although the negative studies suggest caution in such an interpretation.

Additional important risk factors for breast cancer are benign breast disease, in particular the subgroups with proliferative and atypical cell patterns, and family history of breast cancer. These factors generally weigh heavily with clinicians in decisions about prescribing estrogens. Epidemiologic studies, unless specifically designed to test the potential interactions of estrogens with one or another of these risk factors, usually contain insufficient numbers of subjects to produce reliable estimates of risk. Some authors (9, 10, 115, 136) have suggested that estrogens enhance breast cancer risk in women with prior benign breast disease, but two studies with the largest number of relevant subjects have shown no such association (62, 151). A similar equivocal statement could be made about the possible modifying effect of family history (9, 56).

In summary, epidemiologic studies have not consistently demonstrated a causal link between estrogen replacement therapy and breast cancer risk. To the extent that such an association exists, it has been observed primarily with high-dosage estrogen, higher than the 0.625 mg of conjugated estrogens that is usually pre-

scribed daily to relieve menopausal complaints and retard development of osteoporosis. However, even a high-dose effect was not observed in several large, well-designed epidemiologic studies that had sufficient power to detect an association if one existed.

Osteoporosis and Associated Fractures: Beneficial Effect

A role for estrogen in the etiology of osteoporosis has been suggested by the many studies showing that loss of bone mass accelerates in women just after bilateral oophorectomy or natural menopause (21, 23, 54, 71, 88, 96) and by the finding that bilateral oophorectomy without estrogen replacement before natural menopause is associated with an increased risk for hip fracture (70).

Many studies have also shown that estrogen replacement therapy at doses of at least 0.625 mg conjugated estrogen or 1.5 μg ethinylestradiol per day prevents or greatly retards bone loss in peri- and postmenopausal women as long as estrogen is being taken (23, 24, 32, 38, 52, 53, 79, 93, 107, 126). Doses below these levels afford partial protection (38, 53). Following cessation of estrogen use, bone loss occurs at a rate similar to that seen immediately after the menopause in women not treated (25, 82). Results from a randomized trial of an estrogen/progestogen treatment versus a placebo in 94 women who were 6 months to 3 years postmenopausal are shown in Fig. 1 (24). After 2 years of estrogen/progestogen use, some of the women were randomly switched from placebo to treatment and others from treatment to placebo. The preservation of bone mass while on estrogen/progestogen treatment was noted both among those initially assigned to the treatment and among those who started treatment after 2 years. Similarly, the loss of bone mass while on placebo was seen among those initially assigned to placebo and among those assigned to placebo after 2 years on treatment (Fig. 1).

Estrogen replacement therapy also protects against fractures associated with osteoporosis. Several case–control studies (59, 61, 71, 100, 147) have reported that estrogen replacement therapy by peri- or postmenopausal women reduces the

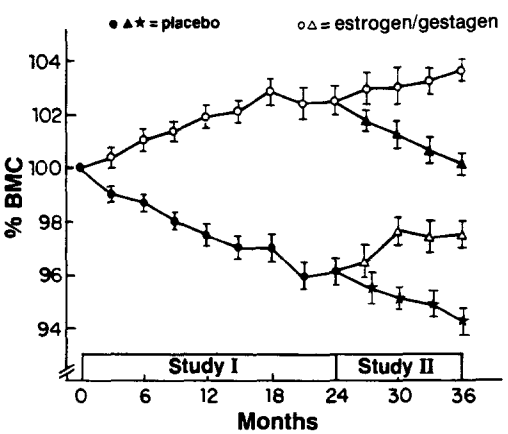

FIG. 1. Bone mineral content (BMC) of the distal forearm as a function of time and treatment in 94 (Study I) and 77 (Study II) women soon after menopause (24).

risk for hip and Colles' fractures by about 50% while the estrogens are being taken. The two case–control studies (100, 147) that considered the effect of dose showed no difference in the degree of protection according to dose. Table 4 shows that, in general, the longer the use, the lower the risk—at least through 6 years of use. Some evidence (147) suggests that much of the protective effect is lost within a few years of stopping estrogen therapy. Replacement estrogens also reduce the risk of vertebral fractures (32, 39, 81, 109).

Thus, studies consistently show that estrogen replacement therapy protects against osteoporosis and associated fractures while the estrogens are being taken. However, several details of the relationship remain to be elucidated. First, since bone loss appears to accelerate around the time of menopause, some would argue that the shorter the interval between onset of menopause and initiation of estrogen use, the more bone mass is preserved (2). Two case–control studies of hip fracture (59, 70), in fact, suggest that use close to the time of menopause affords greater protection than the same extent of use in later years. However, if bone loss accelerates immediately after cessation of use to an extent similar to that immediately following menopause (25, 82), this argument for the importance of starting estrogen therapy immediately after the menopause is not compelling, unless estrogens are to be taken indefinitely. Studies of the extent to which estrogens started several years after menopause retard bone mass loss are needed. Second, the optimal dose of estrogen for maximum benefit is uncertain; evidence is contradictory as to whether doses greater than 0.625 mg of conjugated estrogens or 1.5 μg of ethinylestradiol bring about a further increase in cortical bone mass or decrease in fracture risk (23, 38, 52, 53, 79, 93, 100, 104, 147). Third, whether the addition of cyclic progestogen to the estrogens is more beneficial than estrogens alone, as suggested by short-term trials (24, 25), remains to be determined in long-term trials. Effects of progestogens will be discussed in greater detail below. Fourth, the finding of Weiss *et al.* (147) that the protective effect of estrogen replacement therapy against hip and forearm fractures is lost within a few years after cessation of use needs to be evaluated in other studies, since (as Weiss *et al.* point out) numbers of former users were small in their studies. Also, one would expect that prevention or retardation of bone loss, even temporarily, would result in greater ultimate preservation of bone mass than if loss had continued unabated.

TABLE 4
RELATIVE RISK OF FRACTURE OF THE HIP OR LOWER FOREARM ACCORDING TO DURATION OF USE OF POSTMENOPAUSAL ESTROGEN

Duration of use (years)	Relative risk
No use or <1 year	1.0
1–2	0.8
3–5	0.9
6–9	0.4
>10	0.5

Source: Ref. 147.

Coronary Artery Disease: Probable Beneficial Effect

Cardiovascular diseases (CVDs) are by far the leading cause of death among U.S. women as well as men (140). Thus, even minor changes in CVD risk as a result of estrogen replacement therapy could affect life expectancy in large numbers of women, easily outweighing the effects of changes in risk of other, less-common diseases. Most studies report that estrogen replacement therapy protects against CVD and, in particular, against coronary artery disease (CAD) among women (Table 5). Of 19 studies, 15 show a reduction in risk among estrogen users (1, 13, 20, 45, 47, 73, 86, 94, 102, 103, 105, 116, 131, 133, 134); two studies show no effect (113, 114), and two report an increased risk (60, 149).

In the studies showing a protective effect, the estimated relative risk in estrogen users compared with nonusers varies from about 0.2 to 0.7. Of the two reports showing no effect of estrogen use on CVD risk, one (114) was of women under 50 years of age, who—because of their young age—had experienced infrequent use of estrogen replacement therapy and were at minimal risk for CVD. Only a small, flawed case–control study (60) and the Framingham Study (149) have reported an increased risk for CVD among estrogen users (Relative risk [RR] = 8.44 and 1.76, respectively). The case–control study suffered from various methodologic problems (14), and a reanalysis (30) of the Framingham data using more specific

TABLE 5
STUDIES OF ESTROGEN REPLACEMENT THERAPY AND CARDIOVASCULAR DISEASE

Study	Design	Endpoint[a]	Relative risk	95% Confidence limits	*P*
Lafferty *et al.* (73)	Cohort	MI	0.16	[b]	0.051
MacMahon (86)	Cohort	All CVD	0.30	[b]	[c]
Stampfer *et al.* (131)	Cohort	All CVD	0.30	0.2–0.6	0.001
Nachtigall *et al.* (94)	Trial	MI	0.33	[b]	0.240
Hammond *et al.* (45)	Cohort	All CVD	0.33	[b]	0.001
Potocki (105)	Cohort	All CVD	0.33	[b]	[c]
Bush *et al.* (15, 16)	Cohort	CVD deaths	0.34	0.1–0.9	0.023
Talbott *et al.* (134)	Case–Control	Sudden death	0.34	0.1–3.2	[c]
Burch *et al.* (13)	Cohort	Fatal CAD	0.43	0.2–0.7	[c]
Ross *et al.* (116)	Case–Control	Fatal CAD	0.43	[b]	0.010
Petitti *et al.* (102)	Cohort	CVD deaths	0.50	0.2–0.9	[c]
Henderson *et al.* (47)	Cohort	MI	0.54	[b]	0.007
Szklo *et al.* (133)	Case–Control	Nonfatal MI	0.61	0.2–1.9	[c]
Adam *et al.* (1)	Case–Control	Fatal MI	0.65	0.5–0.9	[c]
Pfeffer *et al.* (103)	Case–Control	MI	0.68	0.3–1.4	0.300
Rosenberg *et al.* (113)	Case–Control	Nonfatal MI	0.97	0.5–2.0	[c]
Rosenberg *et al.* (114)	Case–Control	Nonfatal MI	1.00	0.6–1.7	[c]
Wilson *et al.* (149)	Cohort	All CVD	1.76	[b]	0.010
Jick *et al.* (60)	Case–Control	Nonfatal MI	8.44	4.6–12.3	0.002

[a] MI, myocardial infarction; CVD, cardiovascular disease; CAD, coronary artery disease.
[b] Relative risk cannot be computed from available published data.
[c] *P* value not given.

endpoints showed a protective effect of estrogen use among women 50–59 years (RR = 0.32), and no adverse effects among women 60 years and older (RR = 1.1).

Data on estrogen dose, duration of use, and type of estrogen used in relationship to CAD are generally unavailable in the published reports. Thus, it is unclear whether dose and length of use affect risk. However, some reports showed that women currently using estrogens had a lower risk of CAD than women who had previously used them (93, 116, 131). Effects of recency of use, dose, length of use, age at time of use, and type of compound used are important issues meriting further study.

It is biologically plausible that estrogen replacement therapy protects against the development of CAD. Serum high-density lipoprotein (HDL) is a strong, inverse predictor of CAD, and estrogen use has been shown to raise serum levels of HDL (18, 111, 144). In one report (17), women using moderate doses (0.625 mg) of oral conjugated estrogens had HDL levels approximately 17% higher than women not taking estrogens. Theoretically, this magnitude of increase in HDL levels would correspond to about a 40% reduction in CVD risk.

Oral estrogens tend to reduce low-density lipoprotein (LDL), the atherogenic subfraction of total cholesterol. In the study (17) cited above, estrogen users had LDL levels approximately 7% lower than those of nonusers. Such difference in LDL levels would theoretically correspond to about a 3% reduction in CVD risk among women.

PROGESTINS

To date, relatively few studies of the long-term health effects of menopausal progestational agents have been undertaken. Clinical and biochemical evidence would suggest that progestins counter the adverse effects of estrogens on the endometrium. The published studies of the relation of progestins to breast cancer risk do not permit conclusions to be drawn at this time. Indeed, long-term use, namely for about 2 years or longer, of combination oral contraceptives with relatively high progestin content (i.e., formulations with the equivalent of 2.5 mg or more of norethindrone acetate) reduces the risk of benign breast disease about 50 to 60% (130). As reviewed below, some evidence suggests that progestins given alone can prevent or arrest bone loss, similar to estrogens, and that cyclic progesterone coupled with estrogen may further increase bone mass, at least in the short term. Considerable concern has been voiced over the potential adverse effects of progestins on CVD, mediated by unfavorable changes in lipoprotein fractions associated with progestin use.

Endometrial Cancer: Beneficial Effect of Progestin in Women Taking Estrogens

Estrogen is a growth hormone for endometrial tissue. During the first half of a normal menstrual cycle (proliferative phase), estrogen activates special intracytoplasmic proteins in the endometrial cells. These special proteins or receptors bind estrogen with a high affinity. Each endometrial cell may contain 5,000 to 15,000 of these receptors. The activated estrogen receptor complex stimulates new cell proliferation. Synthesis of progesterone receptors in endometrial cells is

largely dependent on estrogen stimulation. Without the prior estrogen priming, progesterone has little activity on endometrial cells. Progesterone also inhibits estrogen receptor activity as well as the synthesis of progesterone binding sites (5, 40, 46, 69, 89).

Without the addition of progesterone and conversion from proliferative to secretory pattern, the endometrium has a tendency to shed in an irregular and unpredictable fashion. Continued unopposed estrogen stimulation produces the histologic pattern of hyperplasia, which has been shown to advance to adenomatous hyperplasia, carcinoma *in situ,* or eventually to endometrial cancer (12, 34, 42, 44, 84, 101). This progression is well recognized in patients with Stein–Leventhal syndrome (125) and patients with estrogen-producing tumors (43). An elevated risk for endometrial cancer has also been reported in infertile women with disorders characterized by unopposed estrogen production (112). The daily addition of potent synthetic progestogens to the estrogen-primed endometrium produces a markedly altered endometrial response (135). This type of endometrium has a decidual pattern with a tendency to atrophy rather than progress to hyperplasia.

The ability of potent progestogens to produce progressive endometrial atrophy has led to their use as therapeutic agents (67, 68, 148). In addition to their ability to convert adenomatous hyperplasia to normal endometrium, pharmacologic doses of progestogens may be used to treat metastatic adenocarcinoma of the endometrium; this will produce objective regression of the lesions in approximately 30% of patients (33, 108).

Although the evidence for a protective effect of cyclical progestogens in reducing the risk for endometrial neoplasia is compelling, no firm conclusions regarding the most effective progestogen and dosage regimen can be drawn. One commonly suggested regimen is 10 mg of medroxyprogesterone acetate orally for the last 10 days of each cycle. When this progestogen is prescribed in peri- and postmenopausal women 50–60 years of age receiving 0.625 mg conjugated estrogens orally, 97% will experience a 3- to 4-day "menstrual flow." This proportion decreases with increasing age so that by age 65, 60% continue to experience light bleeding (36). This persistent bleeding during the sixth and seventh decades of life is objectionable to some women, making compliance a potential problem even among women who may appreciate the therapeutic benefits of this regimen. With estrogen alone, however, the bleeding is less predictable and therefore also potentially problematic.

Breast Cancer: An Open Question

Several lines of epidemiologic evidence suggest a protective effect of progestin for breast cancer. Women with a history of infertility due to endogenous progesterone deficiency were at increased risk of premenopausal (not postmenopausal) breast cancer compared with women whose infertility was due to nonhormonal causes in one study (27), and women with infertility due to conditions causing unopposed estrogen production were found to have a nonsignificant excess of breast cancer compared to women in the general population in another study (112). In addition, breast cancer risk has been reported to be inversely related to

plasma progesterone levels (92, 118). The preliminary results of an international study showed that progestins administered as injectable contraceptives (depot medroxyprogesterone acetate) were associated with a decreased breast cancer risk (152). Finally, in a nested case–control study, risk for benign breast disease was shown to be inversely related to progesterone dose in oral contraceptives (11).

On the other hand, conflicting evidence is derived from several sources. Epidemiologic investigations have failed to find any evidence of differences in menstrual cycle irregularity among women with breast cancer compared with controls (122) nor differences in luteal phase progesterone levels in women with a history of benign breast disease or breast cancer compared with healthy premenopausal parous women (106). A study that followed 5,000 women receiving injections of medroxyprogesterone for contraception for 4 to 13 years did not exhibit any alteration in breast cancer risk (78). Moreover, the large-scale Contraceptive and Steroid Hormone (CASH) study found no relation of progestogen "potency" of oral contraceptives to breast cancer (130), following an earlier report that breast cancer risk was positively related to the progestin "potency" of oral contraceptives (104, 132).

One widely reported prospective study (35, 37) suggested that women taking postmenopausal estrogen with progestin had a markedly reduced risk for breast cancer compared with women taking estrogens alone or untreated women. The study has been criticized for failure to describe and adjust for important differences among women in the various treatment groups (31, 77). Since it was not a randomized study, women whom physicians chose to treat with progestins may have differed from other women with regard to family and personal history of breast disease and other breast cancer risk factors. A small clinical trial by Nachtigall *et al.* (94) also showed lower breast cancer incidence among women receiving high-dose conjugated estrogens cyclically with progesterone (0/84), when compared with control women (4/84).

Although some data on endogenous progestins and on exogenous progestins in oral contraceptives support the notion that progestins may play a protective role, the evidence is not consistent, and there are no carefully designed, large-scale studies of the potential causal role of exogenous menopausal progestins in breast cancer. At present the evidence would at least suggest that the addition of cyclical progestins to menopausal estrogens will have no adverse affects on breast cancer risk.

Osteoporosis and Associated Fractures: Probable Beneficial Effect

The few available studies of the role of progestins in osteoporosis have been based upon limited sample size, and none have addressed the question of long-term effects. On balance, however, they suggest a beneficial effect. Some evidence indicates that progestins given alone confer protection against osteoporosis (29, 83, 119), and that combined estrogen/progestin regimens have a greater effect than estrogen alone by promoting new bone formation (24, 25, 28, 93, 110). There is no evidence that adding progestins to estrogens negates the beneficial effects of

estrogen given alone. More research is needed of possible differential effects on bone matrix and mineralization by type of progestin administered (80).

Coronary Artery Disease: Potential Increased Risk

The effects of progestins on risk of CAD may be the unresolved issue of greatest potential importance in the menopausal replacement hormone risk–benefit equation. The issue is unresolved because studies of the relationship of menopausal hormones to CAD have been largely limited to unopposed estrogens and have not evaluated the effect of progestin supplementation. However, women who take oral contraceptives that contain relatively high doses of the progestins norethindrone acetate and norgestrel have been reported to be at increased risk for myocardial infarction or stroke compared with women who take lower dose formulations (63, 91).

Serum lipoproteins, a major predictor of CVD risk, appear to be adversely affected by progestins. A variety of studies have shown that progestins are associated with increases in LDL and decreases in HDL. Such effects have been reported for unopposed progestins, for progestins combined with estrogens in various formulations of oral contraceptives (8, 142), and for progestins given to postmenopausal women as a supplement to estrogen replacement therapy (74, 99, 142); the extent of change in lipoproteins was dependent on the type of progestin administered. The vast majority of progestins prescribed for menopausal women are either medroxyprogesterone acetate (Provera), a 17α-hydroxyprogesterone derivative, or the 19-nortestosterone derivatives, mainly norgestrel and norethisterone. Unopposed 19-nor derivatives decrease HDL cholesterol levels substantially, and modestly increase LDL cholesterol levels (72, 123, 143). Although some studies suggest that medroxyprogesterone acetate taken alone may decrease HDL cholesterol levels (123, 138), other investigators have concluded that use of this progestin does not result in the adverse lipoprotein profiles associated with the 19-nor derivatives (127, 128). When the 19-nor agents are added to estrogens, HDL levels are reduced below baseline, i.e., levels are lower than those in women not receiving estrogens (49, 87, 98, 153). When medroxyprogesterone acetate is added to estrogens, the HDL levels approach those of women not receiving estrogens (97, 98, 141). One study, however, showed similar reductions in HDL associated with both levonorgestrel, a 19-nor agent, and medroxyprogesterone acetate (99). A randomized clinical trial of women receiving the progestin norethisterone acetate with estrogens and women on placebo found no differences in serum HDL cholesterol levels, which the authors suggested might be explained by the much lower progestin dose in their study (1 mg/day for 10 days) compared with previous investigations (22). Still, the favorable increase in HDL cholesterol usually seen with estrogens given alone was not observed.

Taken together, the above findings have led some investigators to conclude that progestin doses should be kept to the minimum possible to reduce endometrial cancer risk associated with unopposed estrogen use, or that they be avoided, especially among women who have had a hysterectomy (18) or those who have significant hyperlipidemia (137). Whether the adverse changes in lipoprotein levels associated with progestin use translate into an increased risk for CAD, and

whether that risk is sufficient to outweigh any benefits that accrue by adding progestins to menopausal estrogen therapy are areas that require careful study.

SUMMARY

On balance, for the diseases considered here, estrogen therapy appears to be beneficial for menopausal women, as it probably reduces the risks for CAD and osteoporosis, two of the major causes of mortality and morbidity among postmenopausal women. Although unopposed estrogen therapy increases risk for endometrial cancer, that cancer is relatively rare and is not fatal in the vast majority of cases associated with estrogen use. Definitive conclusions about the relation of menopausal estrogens to breast cancer cannot be drawn. The evidence is inconsistent, and if there is any increase in risk associated with use, it is likely to be small and to apply only to use of high-dose preparations (>0.625 mg). For the most part, the higher-dose preparations should not be necessary for clinical relief of menopausal symptoms, to favorably affect CAD risk, or for prevention of osteoporosis.

There is considerably less consensus on the issue of menopausal progestins. Although evidence from randomized controlled trials is lacking, biochemical and clinical evidence suggests that progestin supplementation is associated with a reduction in endometrial cancer risk among women taking menopausal replacement estrogens. Progestins may augment the beneficial effects of estrogens in providing protection against osteoporosis, although this effect is far from certain at this time. For breast cancer, there is little direct evidence bearing on either a causal or protective role of menopausal progestins.

However, progestins probably unfavorably alter the lipoprotein profile, which may increase a user's risk for CAD, although studies of CAD outcomes are lacking at present. Without knowing the effect of progestin supplementation on CAD, it would be inappropriate to draw any firm conclusions regarding its adoption at this time. Given the relatively high incidence and mortality of CAD in postmenopausal women, even a minor increase in risk, or negation of the benefits associated with unopposed estrogens, would not only cancel but also dramatically outweigh the "benefits" of progestins for other much less common diseases, most notably endometrial cancer. In terms of absolute numbers of lives affected, any negative effects on CAD risk could potentially counterbalance or displace the beneficial effects on all other causes combined.

We conclude that moderate-dose estrogen replacement therapy is of potential benefit to postmenopausal women, but that progestin supplementation requires further study, particularly for CAD risk, before conclusions regarding its use can be drawn. Caution would dictate that if progestins are prescribed, the lowest doses possible to achieve desired effects on the endometrium should be used, with preference given to medroxyprogesterone acetate over the 19-nor steroidal agents. Recommendations for individual patients may vary depending on their risk characteristics, including, among others, family history, lipid profiles, and hysterectomy status. Since there is wide variation in biologic activity among the various progestational agents, future studies should examine the effects on disease by type of progestin, dose, and route of administration.

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