Panel Session: Prevention/Treatment

The Risks and Benefits of Long-Term Estrogen Replacement Therapy

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Synopsis

Estrogen replacement therapy (ERT) for postmenopausal women greatly reduces the risk of osteoporotic fractures, but carries an increased risk of endometrial cancer. This risk can be reduced by the addition of progestin, which does not interfere with the osteoporotic benefit of estrogen. Although long-term use data are few, there is presently little evidence for an increase or decrease in breast cancer risk associated with estrogen by itself (unopposed estrogen), or estrogen plus progestin. In contrast, a large body of evidence suggests that unopposed estrogen significantly reduces the risk of cardiovascular disease; there is no evidence that this benefit will persist when a progestin is added. The preferred method of estrogen replacement therapy, to prevent osteoporosis in a postmenopausal woman with an intact uterus, should be chosen with these different risks and benefits in mind.

In the United States, some form of estrogen replacement therapy (ERT) is prescribed for more than one-quarter of all postmenopausal women, and increasingly that prescription is given in the absence of, or beyond, the period of menopausal symptoms. The rationale for, and risks of, long-term estrogen use are the subject of this review.

Benefit: Osteoporosis

There is little argument that the best documented benefit of ERT is reducing the rate of postmenopausal bone loss, thereby reducing the risk of fracture in later years. Immediate evidence of benefit can be demonstrated in randomized clinical trials by comparing bone loss, measured by single or dual photon absorptiometry, in estrogen- versus placebo-treated women. The inference that delayed bone loss reduces subsequent fracture risk is supported by case-control studies of fracture patients, in whom the estimated relative risk associated with estrogen use for 4 or more years is approximately 50 percent.

Risk: Endometrial Cancer

The major known risk of ERT is endometrial cancer. The risk increases with the estrogen dose, duration of use, and probably the presence of other risk factors for endometrial cancer, such as obesity. Despite considerable debate about the effect of different study designs on the true relative risk, it is generally agreed that unopposed estrogen use, that is, estrogen used without progestin, in the smallest dose that prevents osteoporosis, and used for 5 years or longer, carries at least a fivefold increased risk of endometrial cancer.

Estrogen-associated endometrial cancer is better differentiated, less invasive at diagnosis, and less often fatal than endometrial cancer occurring in women who have not used ERT. Although the incidence of endometrial cancer rose and then fell in relation to the number of noncontraceptive estrogen prescriptions in the United States, the *mortality* rate for endometrial cancer actually decreased during the years when the incidence rose. In fact, some data (*1*) suggest that the overall death rate in estrogen-using women who had endometrial cancer is less than that in women who neither had endometrial cancer nor used estrogen (fig. 1).

Possible Risk: Breast Cancer

Until recently, there was no evidence that ERT was associated with an increased risk of breast cancer. Neither estrogen dose nor duration was consistently

Table 1. Risk of breast cancer by duration of estrogen replacement therapy: results of two large case-control studies

Use	Number of cases	RR[1]	(CI)[2]	Number of cases	RR[1]	(CI)[2]
Never used ...	931	1.00	—	942	1.00	—
Ever used.....	1,029	1.00	(0.9-1.2)	427	1.00	(0.9-1.2)
Years of use:						
Less than 5	486	0.90	(0.8-1.0)	267	1.10	(0.8-1.3)
5-9	249	1.10	(0.9-1.3)	104	1.10	(0.8-1.5)
10-14	159	1.30	(0.9-1.6)	34	0.80	(0.5-1.3)
15-19	70	1.30	(0.9-1.8)	15	1.30	(0.6-2.6)
20+	49	1.50	(0.9-2.3)	7	1.80	(0.6-5.8)

[1]RR = relative risk.
[2]CI = 95 percent confidence interval.

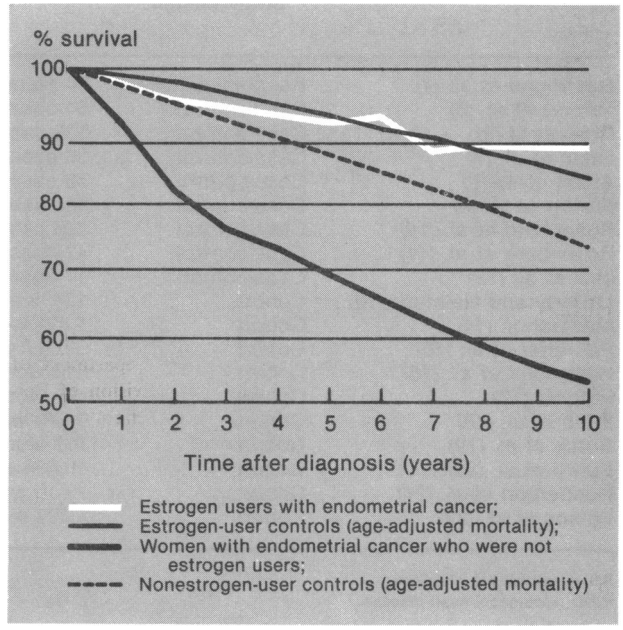
associated with an increased risk of breast cancer in the majority of the numerous reported case-control studies, but very few of these studies included women who had had estrogen treatment for more than 10 years. Demonstration of an estrogen-breast cancer association in diethylstilbestrol users was first apparent after 20 years, suggesting that longer follow-up may be necessary to show an association.

The results of two large case-control studies (*2,3*) suggest an increased risk of breast cancer, first apparent after 15–20 years of ERT (table 1.) In a study of women in whom breast cancer was detected during a multicenter screening program, any use of estrogen carried no increased risk of breast cancer, but use for more than 20 years appeared to double or triple the risk. Similarly, in a population-based case-control study of a large number of women receiving steroid hormones, there was no increased risk until estrogen use continued for 20 years or longer. The 1.8 relative risk in these women was not statistically significant, but only 13 women were in this duration of use group. Until recently, women on extended ERT were primarily those who had had a premature menopause, whether natural or surgical. The reported increased risk with increased duration of ERT is apparent after adjusting for age at menopause. The factors that led to early menopause (natural or surgical) may also be risk factors for breast cancer. Therefore, the conclusion that prolonged estrogen use increases the risk of breast cancer remains tentative, but the possibility is disturbing.

Probable Benefit: Cardiovascular Disease

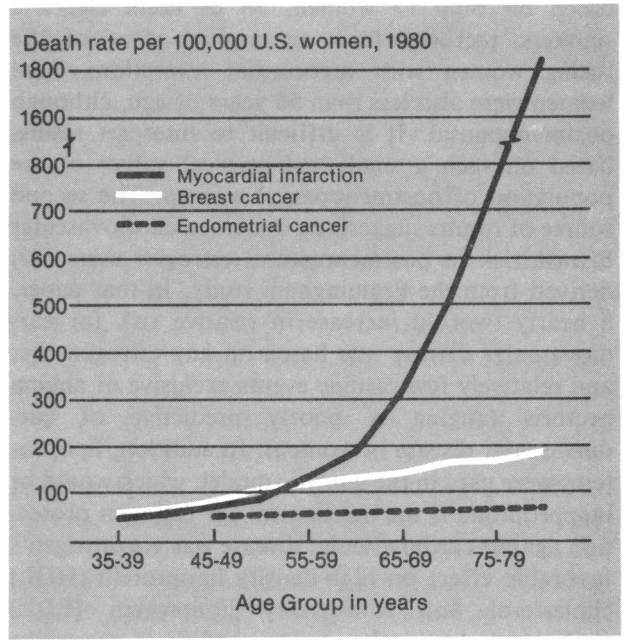
Many investigators (*4–22*) have examined the relationship of ERT to cardiovascular disease in postmenopausal women using a variety of study designs, including case series, case-control studies,

Figure 1. Survival of women with endometrial cancer and history of estrogen use



Source: Reference *1*. Reprinted with permission of the publisher.

Figure 2. Death rates in women from myocardial infarction, breast cancer, and endometrial cancer



Source: Reference *24*.

cohort studies, and one small clinical trial (table 2). Most studies show a reduction of approximately 50 percent in subsequent ischemic heart disease, two (*10,11*) show no association, and two studies (*12,22*) suggest harm. Since the two studies reporting

Table 2. Summary of studies of estrogen replacement and cardiovascular disease

Reference	Study design	Population size	End point	Relative risk	P-value
Nachtigall et al. *(4)*	Randomized trial	84 pairs	Fatal/non-fatal MI[1]	0.33	> .05
Talbott et al. *(5)*	Case-control	64 cases, 64 controls	Sudden death	0.34	> .05
Ross et al *(6)*	Case-control	133 cases, 133 controls	Fatal CHD[2]	0.43	< .01
Szklo et al. *(7)*	Case-control	36 cases, 39 controls	Nonfatal MI	0.61	> .05
Adam et al. *(8)*	Case-control	76 cases, 151 controls	Fatal MI	0.65	> .05
Pfeffer et al. *(9)*	Case-control	185 cases, 511 controls	Fatal/non-fatal MI	0.68	> .05
Rosenberg et al. *(10)*	Case-control	336 cases, 6,730 controls	Nonfatal MI	0.97	> .05
Rosenberg et al. *(11)*	Case-control	477 cases, 1,832 controls	Nonfatal MI	1.00	< .05
Jick et al. *(12)*	Case-control	17 cases, 34 controls	Nonfatal MI	7.5	> .05
Lafferty and Helmuth *(13)*	Cohort	124 women	Fatal/non-fatal MI	0.16	= .05
MacMahon *(14)*	Cohort	1,891 women	All CVD[3]	0.30	—
Stampfer et al. *(15)*	Cohort	32,317 women	All CVD	0.30	< .01
Hammond et al. *(16)*	Cohort	610 women	All CVD	0.33	< .01
Potocki *(17)*	Cohort	198 women	All CVD	0.33	—
Bush et al. *(18)*	Cohort	2,270 women	CVD mortality	0.34	< .05
Burch et al. *(19)*	Cohort	737 women	Fatal CHD	0.43	< .05
Petitti et al. *(20)*	Cohort	16,638 women	CVD deaths	0.50	< .05
Henderson et al. *(21)*	Cohort	7,610 women	Fatal/non-fatal MI	0.54	< .05
Wilson et al. *(22)*	Cohort	1,234 women	All CVD	1.76	< .05

[1]MI = myocardial infarction.
[2]CHD = coronary heart disease.
[3]CVD = cardiovascular disease.
Source: Reference *23*.

increased risk are the exception, they merit careful review.

One of the studies (*12*) that showed a striking increase in relative risk (7.5) is a case-control study based on only 17 women, 16 of them cigarette smokers, recruited from an original group of 107 young women with myocardial infarction; these women were also less than 50 years of age, although postmenopausal. It is difficult to interpret results based on such a small and atypical subset of the population of postmenopausal women. The second source of results suggests an increased cardiovascular disease risk in postmenopausal estrogen users (*22*) derived from the Framingham study. In that paper, a nearly twofold increase in relative risk for cardiovascular disease was based on any estrogen use, and relatively few cardiac events exclusive of angina pectoris (angina is poorly predictive of cardiovascular disease in women). In addition, lipoproteins were used in the analytic model, which would be inappropriate if the mechanism for estrogen protection against cardiovascular disease was via estrogen's favorable effect on high-density lipoprotein (HDL) cholesterol and low-density lipoprotein (LDL) cholesterol. In another analysis of three successive cohorts of Framingham women ages 50–59, which excluded angina as an end point, researchers found that use within the past 10 years was associated with a significantly reduced risk. The increased risk associated with estrogen in Framingham was primarily in older women, and most striking for stroke. It is difficult to balance these results with the lower overall and cardiovascular disease mortality reported in other studies.

None of these studies adequately deals with the probability that women who are prescribed estrogen are healthier, leaner, and of higher social class than women not so treated. Such women are at reduced risk of cardiovascular disease to begin with. In addition, most or all of the women in these studies were treated with conjugated equine estrogen (Premarin), usually given without a progestin, and probably in doses higher than would be recommended today. Therefore, any conclusions about a protective effect of ERT against heart disease cannot necessarily be extrapolated to other estrogens, or to Premarin when used in lower doses or in combination with a progestin.

The Progestin Question

The use of estrogen and progestin in combination, or estrogen in sequence with a progestin, permits the prevention of osteoporosis without the risk of endometrial cancer. Unopposed estrogen causes endometrial hyperplasia in up to two-thirds of postmenopausal users, a small but undefined percentage of whom eventually develop endometrial cancer. Endometrial hyperplasia is prevented by the addition of a progesterone, such as medroxyprogesterone, given in adequate dose (10 milligrams per day) and duration (10–12 days per month).

This regimen does not reduce HDL cholesterol (as occurs with some 19-norprogestins), but it probably modifies the elevation in HDL cholesterol, and the reduction in LDL cholesterol that follows unopposed estrogen. Therefore, the apparent benefit of unopposed estrogen may be lost or reduced with the addition of a progestin. Low doses of progestin have less effect on lipoproteins, but they have not been proven to prevent endometrial hyperplasia. The opinion that postmenopausal estrogen plus a progestin *prevents* breast cancer is unsubstantiated. There are no data on the safety of long-term progestin use in older women.

If unopposed estrogen prevents ischemic heart disease, and if this benefit is negated by concomitant progestin therapy, then a decision favoring estrogen alone or in combination must take into account the benefits and the risks of each regimen. Cancer is a serious complication of any therapy, but it is far less important than ischemic heart disease as a cause of mortality (fig. 2) or morbidity. In 1983, there were 26.6 hospitalizations for ischemic heart disease per 1,000 women 55 years or older in the United States, compared with 1.3 hospitalizations for endometrial cancer in the same population.

Conclusions

Routine estrogen plus progestin is an effective regimen for the prevention or delay of clinically significant osteoporosis, and this treatment probably prevents endometrial cancer. The combination may not prevent ischemic heart disease, as unopposed estrogen may do. The prevention of heart disease, if real, would have far greater consequences for morbidity and mortality than the expected increase in endometrial cancer risk.

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