POSTMENOPAUSAL ESTROGEN THERAPY AND CARDIOVASCULAR DISEASE

Ten-Year Follow-up from the Nurses' Health Study

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Abstract *Background.* The effect of postmenopausal estrogen therapy on the risk of cardiovascular disease remains controversial. Our 1985 report in the *Journal,* based on four years of follow-up, suggested that estrogen therapy reduced the risk of coronary heart disease, but a report published simultaneously from the Framingham Study suggested that the risk was increased. In addition, studies of the effect of estrogens on stroke have yielded conflicting results.

Methods. We followed 48,470 postmenopausal women, 30 to 63 years old, who were participants in the Nurses' Health Study and who did not have a history of cancer or cardiovascular disease at base line. During up to 10 years of follow-up (337,854 person-years), we documented 224 strokes, 405 cases of major coronary disease (nonfatal myocardial infarctions or deaths from coronary causes), and 1263 deaths from all causes.

Results. After adjustment for age and other risk factors, the overall relative risk of major coronary disease in women currently taking estrogen was 0.56 (95 percent confidence interval, 0.40 to 0.80); the risk was significantly reduced among women with either natural or surgical menopause. We observed no effect of the duration of estrogen use independent of age. The findings were similar in analyses limited to women who had recently visited their physicians (relative risk, 0.45; 95 percent confidence interval, 0.31 to 0.66) and in a low-risk group that excluded women reporting current cigarette smoking, diabetes, hypertension, hypercholesterolemia, or a Quetelet index above the 90th percentile (relative risk, 0.53; 95 percent confidence interval, 0.31 to 0.91). The relative risk for current and former users of estrogen as compared with those who had never used it was 0.89 (95 percent confidence interval, 0.78 to 1.00) for total mortality and 0.72 (95 percent confidence interval, 0.55 to 0.95) for mortality from cardiovascular disease. The relative risk of stroke when current users were compared with those who had never used estrogen was 0.97 (95 percent confidence interval, 0.65 to 1.45), with no marked differences according to type of stroke.

Conclusions. Current estrogen use is associated with a reduction in the incidence of coronary heart disease as well as in mortality from cardiovascular disease, but it is not associated with any change in the risk of stroke. (N Engl J Med 1991; 325:756-62.)

THE influence of exogenous hormones on the risk of cardiovascular disease has long been controversial. More than 20 studies published in the past decade have addressed the issue of postmenopausal estrogen use and coronary disease.[1] Our earlier report of a benefit from estrogen use in terms of the risk of coronary disease, based on four years of follow-up,[2] was accompanied by a report from the Framingham Study that came to the opposite conclusion.[3] These disparate findings led to considerable confusion.[4] We now report results for both coronary disease and stroke, based on 10 years of follow-up in the Nurses' Health Study, a large cohort study that included 48,470 postmenopausal women with 337,252 person-years of follow-up.

METHODS

The Nurses' Health Study Cohort

The Nurses' Health Study began in 1976, when 121,700 female registered nurses in the United States completed questionnaires sent to them by mail about their medical history, including previous cardiovascular disease, menopause, diabetes, hypertension, high serum cholesterol levels, and parental myocardial infarction. We included questions on height, weight, smoking, the use of postmenopausal hormones, and the use of oral contraceptives.[5] Every two years, follow-up questionnaires were mailed to obtain updated information and identify newly diagnosed major illnesses. A dietary questionnaire was added in 1980.[6]

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Ascertainment of Estrogen Use

In 1976 the women were asked whether they had taken hormone supplements after menopause, and if so, for how long. Information on hormone use, including the type taken, was updated in the subsequent questionnaires sent every two years through 1986, with explicit questions about current use and duration of use in the intervening period. Because no information on current use was explicitly requested on the 1976 questionnaire, we considered women to have been current estrogen users for the 1976–1978 period if the duration of their estrogen use was equal (within 12 months) to the interval between menopause and the date of completion of the questionnaire. Women whose duration of hormone use was more than 12 months shorter than this interval were considered former users. The daily dose of conjugated estrogens was obtained beginning in 1980.

Identification and Confirmation of Cardiovascular End Points

The study end points included nonfatal myocardial infarction, fatal coronary heart disease, coronary-artery bypass grafting or angioplasty, fatal and nonfatal stroke, total cardiovascular mortality, and deaths from all causes after the return of the 1976 questionnaire but before June 1, 1986. Nurses who reported having a nonfatal myocardial infarction or stroke on a follow-up questionnaire were asked for permission for a study investigator to review their medical records. Nonfatal myocardial infarctions were considered confirmed by hospital records if they met the World Health Organization criteria[7] (i.e., symptoms plus either cardiac-enzyme elevations or diagnostic electrocardiographic changes). Myocardial infarctions that required hospitalization and for which confirmatory information was obtained by interview or letter, but for which no medical records were obtainable, were designated as probable. Thus, infarc-

tions of indeterminate duration discovered on routine examination were not included. Coronary-artery surgery was ascertained by the participants' reports alone.

Nonfatal strokes were considered confirmed by a review of medical records if they were characterized by a typical neurologic deficit, rapid in onset and lasting at least 24 hours, and if they met the criteria of the National Survey of Stroke.[8] We classified strokes as ischemic strokes (thrombotic or embolic occlusion of a cerebral artery), subarachnoid hemorrhages, or intraparenchymal hemorrhages. We excluded subdural hematomas and strokes caused by infection or neoplasia. Strokes reported on the questionnaires that required hospitalization and were confirmed by information from a letter or telephone call, but for which the medical records were unavailable, were designated as probable.

Most deaths were reported by the participants' families. We used the National Death Index[9] to identify deaths among the nonrespondents to each two-year questionnaire; the mortality follow-up was more than 98 percent complete. For all deaths possibly attributable to cardiovascular causes, we requested permission from the next of kin (subject to state regulations) to review the medical records. Deaths were considered to be due to coronary disease if the medical records or autopsy findings confirmed that a fatal myocardial infarction had occurred. The category of coronary death also included cases in which coronary disease was listed on the death certificate as the underlying cause without another, more plausible cause and in which the nurse was known (e.g., on the basis of the hospital record or an interview with her next of kin) to have had coronary disease before death. In no case was the cause listed on the death certificate used as the sole criterion for a determination of coronary death. We classified strokes as fatal if they were documented by autopsy findings or hospital records or if stroke was listed as the underlying cause of death on the death certificate.

The category of cardiovascular mortality included deaths from stroke, deaths from coronary disease, sudden deaths (death within one hour of the onset of symptoms in an apparently healthy woman), and deaths for which coronary disease was listed as the underlying cause and no more plausible cause could be assigned, but for which confirmation was lacking. Major cardiovascular disease was defined to include both death from cardiovascular disease and nonfatal myocardial infarction and stroke. All the interviews and reviews of medical records were conducted without the investigators' knowledge of the category of estrogen use.

Population for Analysis

Women for whom information on hormone use was missing (3.6 percent of all respondents) were excluded from the analysis. Because women with diagnosed cardiovascular disease may alter their hormone use and are also at increased risk for progression of the disease, their inclusion could distort the results. We therefore excluded from the analysis all women who reported a diagnosis of any cardiovascular disease or cancer (except skin cancer other than melanoma) on the 1976 questionnaire. Similarly, women who reported such a diagnosis on a subsequent questionnaire were excluded from further analysis. Thus, at the start of each two-year interval, the base population included no women reporting these diagnoses. For the analyses of mortality from all causes, however, these women were included, so that deaths due to illnesses lasting more than two years could be considered.

We classified women as postmenopausal from the time they reported having a natural menopause or undergoing hysterectomy with bilateral oophorectomy. Women who underwent hysterectomy without bilateral oophorectomy were considered postmenopausal when they reached the age at which natural menopause had occurred in 90 percent of the cohort (54 years for smokers and 56 for nonsmokers). The women's reports of reaching menopause were highly accurate in this cohort.[10]

In 1976, a total of 22,950 postmenopausal women entered the analysis for the 1976–1978 period. The population was expanded to include women who became postmenopausal subsequently and were free of cancer and cardiovascular disease. During the 10-year period from 1976 through June 1, 1986, we accrued 337,854 person-years of follow-up among 48,470 women. The follow-up of the cohort, calculated as a percentage of the total potential person-years of follow-up, was 88.4 percent complete for nonfatal outcomes; for mortality, it was more than 98 percent complete. Follow-up rates were quite similar within the different categories of hormone use.

Statistical Analysis

For each participant, person-months were allocated to the categories of hormone use according to the data reported in 1976 and updated at each two-year interval according to information obtained subsequently. Follow-up for a participant ended with a diagnosis of cardiovascular disease or death. If no questionnaire was returned for a two-year follow-up period, the most recent data were applied to the subsequent follow-up interval. If a woman's previous status had been current hormone use, however, she was classified in the update as having used hormones at some time, but current or former use was not specified.

We calculated the relative risk associated with hormone use, defined as the incidence rate of cardiovascular disease among hormone users (estimated as the number of events divided by the person-time of follow-up for the hormone users) divided by the corresponding rate among women who had never used hormones. Age-specific rates of cardiovascular disease for users and nonusers were calculated in five-year categories and used to compute age-adjusted relative risks with 95 percent confidence intervals.[11] To adjust for a number of risk factors simultaneously, we used proportional-hazards models.[12] All P values are two-tailed.

Results

Women currently using postmenopausal hormones accounted for 21.8 percent of the total follow-up time of 337,854 person-years. Former hormone users accounted for 25.2 percent of the time, and women who had never used hormones 53 percent. In all three groups, potential risk factors for cardiovascular disease were distributed in generally similar patterns. Table 1 shows the age-standardized proportions of

Table 1. Distribution of Characteristics and Coronary Risk Factors Reported by the Women in the Cohort, According to Postmenopausal Hormone Use, with Standardization for Age.*

Variable	Hormone Use		
	current	former	none
	percent of subjects		
Parental MI before the age of 60	10.6	10.0	9.3
Hypertension	23.2	25.0	21.8
Diabetes mellitus	2.7	3.8	3.5
High serum cholesterol	9.9	11.2	7.6
Current smoker (15–24 cigarettes/day)	11.2	14.7	14.5
Quetelet index ≥29†	9.8	13.3	15.0
Bilateral oophorectomy	50.3	39.3	9.3
Past use of oral contraceptives	34.0	27.6	23.9
Vigorous physical activity ≥1 time/week‡	48.2	43.1	42.4
	grams per day		
Mean dietary intake‡§			
Saturated fat	27.6	26.2	26.7
Cholesterol	0.32	0.32	0.32
Polyunsaturated fat	8.9	8.7	8.7
Dietary fiber	17.3	17.2	16.8
Alcohol	7.9	7.5	7.3

*Data are standardized to the age distribution of the person-years of follow-up for the cohort, from 1976 through 1986. MI denotes myocardial infarction.

†The Quetelet index was calculated by dividing the weight in kilograms by the square of the height in meters.

‡As assessed in 1980 and standardized to the age distribution of the cohort at that time.

§Adjusted for energy intake.

Table 2. Relative Risk of Cardiovascular Disease among Current and Former Postmenopausal Hormone Users, as Compared with Those Who Never Used Postmenopausal Hormones, after Adjustment for Age and Multiple Risk Factors.*

Group†	No. of Person-Years	Major Coronary Disease		Fatal Cardiovascular Disease		Total Stroke		Ischemic Stroke		Subarachnoid Hemorrhage	
		No. of cases	RR (95% CI)	No. of cases	RR (95% CI)	No. of cases	RR (95% CI)	No. of cases	RR (95% CI)	No. of cases	RR (95% CI)
No hormone use	179,194	250	1.0	129	1.0	123	1.0	56	1.0	19	1.0
Current hormone use	73,532										
Adjusted for age	—	45	0.51 (0.37–0.70)	21	0.48 (0.31–0.74)	39	0.96 (0.67–1.37)	23	1.26 (0.78–2.02)	5	0.80 (0.30–2.10)
Adjusted for age and risk factors	—		0.56 (0.40–0.80)		0.61 (0.37–1.00)		0.97 (0.65–1.45)		1.46 (0.85–2.51)		0.53 (0.18–1.57)
Former hormone use	85,128										
Adjusted for age	—	110	0.91 (0.73–1.14)	55	0.84 (0.61–1.15)	62	1.00 (0.74–1.36)	34	1.14 (0.75–1.74)	12	1.42 (0.70–2.90)
Adjusted for age and risk factors	—		0.83 (0.65–1.05)		0.79 (0.56–1.10)		0.99 (0.72–1.36)		1.19 (0.77–1.86)		1.03 (0.47–2.25)

*RR denotes relative risk, and CI confidence interval.

†Women with no hormone use served as the reference category in this analysis. The risk factors included in the multivariate models were age (in five-year categories), cigarette smoking (none, former, current [1 to 14, 15 to 24, and ≥25 cigarettes per day]), hypertension (yes, no), diabetes (yes, no), high serum cholesterol level (yes, no), parental myocardial infarction before the age of 60 (yes, no), Quetelet index (in five categories), past use of oral contraceptives (yes, no), and time period (in five two-year periods).

women who reported various characteristics and coronary risk factors according to their estrogen-use status, on the basis of cumulative person-years from 1976 through 1986. Table 1 also shows the mean intake of various nutrients, with adjustment for energy intake,[13] and the proportion of women reporting a period of vigorous exercise at least once per week, both of which were ascertained in 1980. Estrogen users were less likely to have diabetes and more likely to be lean, to engage in regular, vigorous physical activity, to have had a surgical menopause, and to have used oral contraceptives in the past.

Among the postmenopausal women who reported no previous cardiovascular disease, we documented 293 nonfatal myocardial infarctions (228 confirmed and 65 probable), 112 confirmed deaths from coronary disease, and 224 strokes (52 fatal and 172 nonfatal; 177 confirmed and 47 probable) during the 10 years of follow-up. Of the strokes, 113 were ischemic strokes and 36 were subarachnoid hemorrhages; the remaining strokes were of other or unknown types. There were 41 other deaths from cardiovascular causes, for a total of 205 cardiovascular deaths. Coronary-artery surgery or angioplasty was reported by 185 women. In the analyses of total mortality, which included women in whom illnesses developed during follow-up, there were 1263 deaths from all causes. No material differences were observed in any of the analyses between the confirmed and the probable categories of myocardial infarction and stroke or between the fatal and the nonfatal categories of coronary disease or stroke; we therefore merged these categories into two larger categories: major coronary disease (nonfatal myocardial infarction and death from coronary causes) and total stroke.

Overall, the age-adjusted risk of major coronary disease among current estrogen users was about half that of women who had never used estrogen, with a relative risk of 0.51 (95 percent confidence interval, 0.37 to 0.70; $P<0.0001$) (Table 2). For former users, the age-adjusted relative risk was 0.91 (95 percent confidence interval, 0.73 to 1.14; $P = 0.42$). In contrast, we observed no association between current estrogen use and total stroke. The age-adjusted relative risk was 0.96 (95 percent confidence interval, 0.67 to 1.37) and was virtually unchanged after further adjustment for other cardiovascular risk factors. No material associations were observed for ischemic stroke or subarachnoid hemorrhage; there were too few cases of intraparenchymal hemorrhage for analysis.

We observed no apparent association between estrogen use and the incidence of coronary-artery surgery. Among the current users, the age-adjusted relative risk was 1.21 (95 percent confidence interval, 0.84 to 1.73), and for former users it was 0.86 (95 percent confidence interval, 0.60 to 1.22). Among the former users, there were no notable trends with regard to duration of use or time since most recent use. Simultaneous adjustment for other risk factors in multivariate analyses had virtually no effect on these estimates. We found no evidence to suggest that the degree of protection associated with current estrogen use was related to the duration of use, independent of age, for any of the end points; among the former users, the period of time since the cessation of estrogen use was not consistently related to the risk of cardiovascular outcomes (data available elsewhere*).

The study had insufficient statistical power to determine the effects of specific forms of hormone therapy other than unopposed oral conjugated estrogen. Of the 57,570 person-years of follow-up for current hormone users from 1978 through 1986, 71.5 percent involved the use of unopposed oral conjugated estrogen, 11.5 percent other estrogens, 2.7 percent estrogens with progestin, 2.2 percent other hormones, and 12

*See NAPS document no. 04890 for eight pages of supplementary material. Order from NAPS c/o Microfiche Publications, P.O. Box 3513, Grand Central Station, New York, NY 10163-3513. Remit in advance (in U.S. funds only) $7.75 for photocopies or $4 for microfiche. Outside the U.S. and Canada add postage of $4.50 ($1.50 for microfiche postage). There is a $15 invoicing charge on all orders filled before payment.

percent hormones of unknown type (or information was missing). The age-adjusted relative risk of major coronary disease with current use of unopposed oral conjugated estrogen was 0.40 (95 percent confidence interval, 0.26 to 0.62).

Information about the dose of conjugated estrogen was available for the period from 1980 through 1986. The only marked difference in the association observed with different dose levels was an apparent increase in the risk of coronary disease among women taking more than 1.25 mg per day (relative risk, 2.8; 95 percent confidence interval, 0.9 to 8.2), as compared with the substantial decrease in risk among those taking lower doses. The use of estrogen at doses of more than 1.25 mg per day was very uncommon (4 percent of the cohort), however, and the relative risk is based on only three cases.

We assessed whether the inverse association of estrogen use with the risk of coronary disease differed for women with different characteristics. We observed few marked differences in the associations. The age-specific relative risk appeared to show a nonsignificant trend ($P = 0.19$) toward more protection from coronary disease among younger postmenopausal hormone users. For the oldest age group, women 60 to 64 years of age, the relative risk was 1.35 (95 percent confidence interval, 0.65 to 2.82). We noted possible tendencies toward more protection among smokers than among nonsmokers, among women without a parental history of myocardial infarction before the age of 60, and among the leanest women, but these differences in relative risks were not statistically significant.* Among the women who had a natural menopause, the age-adjusted relative risk of major coronary disease for current estrogen users was 0.62 (95 percent confidence interval, 0.39 to 0.97), not as low as the risk for women who underwent bilateral oophorectomy (relative risk, 0.40; 95 percent confidence interval, 0.22 to 0.73).

To evaluate the effect of estrogen use among women at low risk, we defined a subgroup of women who were not current smokers; had no hypertension, diabetes, or high serum cholesterol level; and had a Quetelet index below 32, the 90th percentile for this cohort. For this group, the age-adjusted relative risk of major coronary disease among current hormone users was 0.53 (95 percent confidence interval, 0.31 to 0.91).

To adjust for the effects of several potential risk factors simultaneously, we used proportional-hazards models to estimate the relative risks associated with current and former use of estrogens, controlling for age, follow-up period, and the characteristics listed in Table 1. Because the current estrogen users were slightly healthier, this adjustment attenuated the apparent benefit slightly. The results (shown as adjusted for age and risk factors) were similar to those obtained after adjustment for age alone; for major coronary disease, the relative risk among current users was 0.56 (95 percent confidence interval, 0.40 to 0.80) (Table 2). A model that also included age at menopause as a continuous variable yielded virtually the same estimates. Similar models that included the data on dietary intake and physical activity yielded similar findings, although the estimates were less precise because only data for 1980 through 1986 could be included.

To assess whether receiving more medical care might account for the benefit in postmenopausal estrogen users, we repeated the analysis, limiting it to women who reported having visited a physician in 1978 (65 percent of the cohort). The results were similar to those for the population as a whole: the age-adjusted relative risks of major coronary heart disease were 0.45 (95 percent confidence interval, 0.31 to 0.66) for current estrogen users and 0.79 (95 percent confidence interval, 0.60 to 1.05) for former users. For cardiovascular mortality, the age-adjusted relative risks were 0.52 (95 percent confidence interval, 0.40 to 0.69) for current users and 0.77 (95 percent confidence interval, 0.62 to 0.95) for former users.

In analyzing mortality from all causes, we focused primarily on women who had used estrogen at any time, in order to avoid the potential problem created by shifts in status from current to former use as a result of a diagnosis of disease. We also eliminated the requirement that the cohort be free of diagnosed cancer and heart disease at the beginning of each two-year period; this allowed us to include deaths due to illnesses lasting more than two years. Thus, in this analysis, the cohort was free from diagnosed cancer and heart disease at base line in 1976 (or at entry into the analysis, for those who became postmenopausal later) and was followed until death or the cutoff date of May 31, 1986. For women who had used estrogens at any time, the age-adjusted relative risk of mortality from all causes was 0.81 (95 percent confidence interval, 0.72 to 0.91; $P = 0.0004$); for cardiovascular mortality, it was 0.68 (95 percent confidence interval, 0.52 to 0.90). After adjustment for other risk factors, the relative risks were slightly attenuated, but they remained statistically significant; for total mortality, the risk was 0.89 (95 percent confidence interval, 0.78 to 1.00), and for cardiovascular mortality it was 0.72 (95 percent confidence interval, 0.55 to 0.95; $P = 0.02$). Because in the earlier analyses benefits had been found to be attributable to current estrogen use, this analysis underestimated the benefit of estrogen by including former users with current users. To remove this bias in part, we excluded women who had already discontinued estrogen use at base line but not those who used estrogen at base line and discontinued it later. The exclusion of the latter group would have led to an overestimate of the benefit, because estrogen therapy is often discontinued in women who have potentially fatal illnesses, such as breast cancer.

Discussion

In this prospective study of 48,470 women, we observed that when current postmenopausal estrogen users were compared with women who had never used estrogen, they had about half the risk of major coronary disease or fatal cardiovascular disease and no

increase in the risk of stroke. The prospective study design virtually eliminated the biases in recall and selection that can affect case–control studies. The follow-up rate was high, particularly for fatal outcomes, reducing the likelihood that differential follow-up could have affected the results.

Information on exposure to estrogen and other potential risk factors was derived from reports by the women themselves, but we believe them to be reliable. The reports have been validated by a review of the medical records and by direct measurement with respect to several conditions.[6,14] Also, the risk factors reported by the subjects were strong predictors of subsequent cardiovascular disease,[2,5,15,16] and the subjects were all registered nurses with a demonstrated interest in medical research.

The most plausible alternative to a cause–effect relation between estrogen use and the reduced risk of coronary disease is that healthier women are selected for such therapy. In this cohort, however, the estrogen users appeared only slightly healthier than the nonusers and were generally similar to them with respect to most cardiovascular risk factors. The estrogen users had a much higher incidence of bilateral oophorectomy, a coronary risk factor only for women not receiving estrogen-replacement therapy.[17,18] The estrogen users also tended to be leaner, which may result in lower levels of estrogen from adipose tissue.[19] The likelihood of lower levels of endogenous estrogen in thinner women is consistent with the trend toward a greater benefit from postmenopausal estrogen with respect to coronary disease in that group, but the protection associated with estrogen use was present in women in all categories of the Quetelet index. The stratified and multivariate proportional-hazards models indicated only minor overall confounding, as judged by the similarity of the relative risks after adjustment for age alone with those that took account of other risk factors. The similar benefit in the analysis limited to women who reported a recent visit to a physician suggests that access to medical care appeared to have little effect on estimates of the effect of estrogen on the risk of cardiovascular disease.

The apparent marked benefit of estrogen in reducing the risk of coronary disease is consistent with previous evidence. Of 15 other prospective studies, 14 found decreased risks among estrogen users.[1] The Framingham Study alone found an elevated risk,[3] which was not statistically significant when women with angina were omitted. A subsequent reanalysis of the Framingham data showed a nonsignificant protective effect among younger women but a nonsignificant adverse effect among older women.[20] Similarly, all three cross-sectional studies of coronary angiography showed substantially less atherosclerosis among estrogen users.[21-23] A quantitative overview of previous studies taken together yielded a relative risk of 0.56 (95 percent confidence interval, 0.50 to 0.61); when only the analytic prospective and angiographic studies were considered, the relative risk was 0.50 (95 percent confidence interval, 0.43 to 0.56).[1]

The nonsignificant trend in our data toward a decreasing benefit of estrogen with increasing age is consistent with the Framingham data,[3,20] but Henderson et al. found a substantial reduction in risk among women in their 70s.[28] Future follow-up will clarify this issue, but the weight of the evidence suggests a protective effect among postmenopausal women of all ages. In the analysis of women with a favorable risk-factor profile, the observed age-adjusted relative risk of major coronary disease, 0.53, was virtually identical to that for the whole cohort. This implies that women at lower risk enjoy the same relative benefit from estrogen as women in general. Because rates of coronary disease were lower among the low-risk women, however, the same relative decrease corresponded to a smaller reduction in the number of events.

As in other studies,[1] we found that the benefit of therapy was evident primarily among current estrogen users, and there was no indication of an effect of the duration of use independent of age. The best-supported mechanism is the markedly favorable effect of estrogen on serum lipids: estrogens raise the level of high-density lipoprotein cholesterol and lower that of low-density lipoprotein cholesterol. Although estrogen-induced changes in lipid metabolism are sufficient to explain a large reduction in the risk of coronary disease,[24] other plausible mechanisms have been proposed.[25] We observed less benefit, and perhaps an adverse effect, among women taking more than 1.25 mg of estrogen daily. Such high doses were common in the Framingham cohort, which may partly explain their discrepant results.

The absence of an association between estrogen use and the incidence of coronary-artery surgery was unexpected, particularly in view of evidence from cross-sectional angiographic studies showing a strong association of estrogen use with a reduction in atherosclerosis.[21-23] Perhaps women taking estrogens under closer medical supervision are more likely to undergo coronary surgery when they have a given level of symptoms than women not taking estrogens.

We found no effect of estrogens on the incidence of total stroke or that of ischemic stroke and subarachnoid hemorrhage. In the Leisure World Study, Paganini-Hill et al.[26] did find a decrease in risk, but the benefit may have been overestimated because patients with previous cardiovascular disease, who may be more prone to strokes and less likely to have estrogen prescribed, were not excluded. However, this can explain only part of the observed benefit. The Framingham Study[3] found an adverse effect of using estrogen at any time on the risk of stroke, whereas the large, prospective Copenhagen Study[27] found little effect either way. Both the Copenhagen Study and our own study included mostly middle-aged women, as compared with the Leisure World Study,[26] in which the median age was 73; perhaps the protective effect is limited to older women.

In analyses of total mortality, it is important to exclude subjects at the start of follow-up who have life-threatening diseases. Because women with such diseases (e.g., breast cancer) are both less likely to be prescribed estrogen and more likely to die within a given period, their inclusion in an analysis would exaggerate any benefit of estrogen. Similarly, an analysis restricted to women who continue to use estrogen would have the same effect, because women who acquire certain life-threatening conditions may be advised to cease hormone use. In our analysis, which took those considerations into account, we observed an age-adjusted relative risk of 0.81 (95 percent confidence interval, 0.72 to 0.91) and a multivariate relative risk of 0.89 (95 percent confidence interval, 0.78 to 1.00). The relative risk of cardiovascular mortality in women with any estrogen use, after adjustment for other risk factors, was 0.72 (95 percent confidence interval, 0.55 to 0.95). The benefit with respect to mortality from all causes is likely to be an underestimate, because the effects of estrogen-induced protection from hip fracture and its associated mortality would be more pronounced at an older age. Indeed, in the Leisure World Study, a relative risk of 0.64 (95 percent confidence interval, 0.52 to 0.78) was found for total mortality among current estrogen users,[28] but this was probably an overestimate of the true benefit, because women with prevalent disease were not omitted at base line. Bush et al. reported a relative risk of 0.54 among estrogen users for mortality from all causes,[29] but their result may also have overestimated the benefit, for the same reason. Petitti et al. reported a relative risk of total mortality of 0.8 (95 percent confidence interval, 0.6 to 1.1) in a follow-up study of healthy women.[30]

The consistency of the epidemiologic data, the apparent absence of important confounding or selection bias, and biologic plausibility[24,25] all suggest a causal association between estrogen use and a reduced risk of coronary disease. Further work is needed to identify the women most likely to benefit from hormone therapy, as well as the effect of added progestins. Proposed clinical trials among women with established coronary disease will be useful. The findings regarding mortality from all causes as well as risk–benefit analyses[31-33] suggest that, overall, the benefits of postmenopausal estrogen therapy outweigh the risks,[34] even apart from the substantial benefits in alleviating menopausal symptoms. These risks include an increase in the rate of endometrial cancer, which can be completely or largely blocked by the addition of a progestin, and possibly some increase in the incidence of breast cancer.

The risk–benefit assessment will differ according to a given woman's medical condition and nonmedical characteristics (including the fear of cancer), so we make no global recommendations. The decision must be made by the individual woman and her physician after they evaluate all the relevant benefits and risks.

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