A PROSPECTIVE STUDY OF POSTMENOPAUSAL ESTROGEN THERAPY AND CORONARY HEART DISEASE

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Abstract To clarify the possible role of postmenopausal estrogen use in coronary heart disease, we surveyed 121,964 female nurses, aged 30 to 55 years, with mailed questionnaires, beginning in 1976. Information on hormone use and other potential risk factors was updated and the incidence of coronary heart disease was ascertained through additional questionnaires in 1978 and 1980, with a 92.7 per cent follow-up. End points were documented by medical records. During 105,786 person-years of observation among 32,317 postmenopausal women who were initially free of coronary disease, 90 women had either nonfatal myocardial infarctions (65 cases) or fatal coronary heart disease (25 cases).

As compared with the risk in women who had never used postmenopausal hormones, the age-adjusted relative risk of coronary disease in those who had ever used them was 0.5 (95 per cent confidence limits, 0.3 and 0.8; P = 0.007), and the risk in current users was 0.3 (95 per cent confidence limits, 0.2 and 0.6; P = 0.001). The relative risks were similar for fatal and nonfatal disease and were unaltered after adjustment for cigarette smoking, hypertension, diabetes, high cholesterol levels, a parental history of myocardial infarction, past use of oral contraceptives, and obesity. These data support the hypothesis that the postmenopausal use of estrogen reduces the risk of severe coronary heart disease. (N Engl J Med 1985; 313:1044-9.)

THE possible role of exogenous estrogens in coronary heart disease has been controversial for decades. The observations that premenopausal women are at lower risk for coronary disease than postmenopausal women and that estrogens favorably influence serum lipid levels[1-3] led investigators to test estrogen in a trial among men with a prior myocardial infarction.[4] However, estrogen therapy was stopped when an excess of coronary disease was observed.[4,5] One case–control study in women showed an elevated risk of coronary disease among estrogen users,[6,7] but several recent investigations have found an inverse association.[8,9] In the United States, postmenopausal hormones are used by 2 to 3 million women.[10] Even a small effect of estrogens would have important public health consequences because heart disease is the chief cause of death among women in this country. We therefore examined the effect of hormones on the risk of nonfatal myocardial infarction and fatal coronary disease in a large prospective cohort of postmenopausal women.

METHODS

The Nurses' Health Study Cohort

The Nurses' Health Study cohort was assembled in 1976 when questionnaires were mailed to all female, married, registered nurses aged 30 to 55 who were living in 1 of 11 large U.S. states.[11] The questionnaires sought information on a variety of health conditions, including prior coronary disease (myocardial infarction or angina pectoris), menopause (natural or induced), diabetes, hypertension, high serum cholesterol levels, and a parental history of myocardial infarction. In addition, there were questions on height and weight, current and past smoking, use of oral contraceptives, and use of postmenopausal hormones. A total of 121,964 women completed the questionnaire. In 1978 and 1980, we sent out follow-up questionnaires that updated the information on most of these variables and inquired about the development of new illnesses, including myocardial infarction.

In 1976 the subjects were asked whether they had used postmenopausal hormones after menopause and, if so, for how long. Women were considered current users if the duration of use was equal (within 12 months) to the interval between menopause and the time the questionnaire was completed. Women whose duration of use was less than the interval between menopause and the return of the questionnaire (by more than 12 months) were considered past users. Information on hormone use was updated in 1978 with explicit questions about current use and the duration of use between 1976 and 1978.

The end points for this study were nonfatal myocardial infarction and fatal coronary heart disease. Nurses reporting nonfatal myocardial infarction on the 1978 or 1980 questionnaires were asked to grant permission for a review of their medical records. An incident case was considered confirmed if it occurred after return of the 1976 questionnaire but before June 1, 1980, and was verified in the medical record, according to the World Health Organization criteria[12] of symptoms and either typical electrocardiographic changes or elevations of serum cardiac enzyme levels. Thus, "silent" infarctions and infarcts of indeterminate age that were discovered on routine examination were excluded. Myocardial infarctions that required hospitalization and were corroborated by additional confirmatory information but for which the records could not be obtained were designated as probable.

Most deaths were reported by the subject's next of kin or by postal authorities. After each follow-up questionnaire, we searched state vital records for deaths among the nonrespondents. By comparing ascertainment from independent sources, we estimated that 96 per cent of all deaths were identified. A death was considered to be due to coronary disease if a fatal myocardial infarction was confirmed by hospital records or autopsy. The category of coronary death also included cases in which coronary disease was listed as the underlying cause, without another plausible cause, on the death certificate and the nurse was known (e.g., from the hospital record or an interview with her next of kin) to have had this disease before death. In no case was the statement of cause on the death certificate used as the only criterion to confirm a coronary death. All record reviews (whether or not the subject had died) were conducted by experienced physicians without knowledge of any of the exposure variables. Since sudden death can often occur in the absence of coronary disease, we did not include cases of sudden death unless there was other evidence of coronary disease. Each participant was counted for only one end point.

Since women with a diagnosis of coronary disease may alter their pattern of hormone use and are also at increased risk for progression of the disease, their inclusion could have distorted our results.

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Therefore, nurses who reported either myocardial infarction or angina on the 1976 questionnaire were excluded. Similarly, women with such reports on the 1978 questionnaire were excluded from follow-up after 1978, so that the base population for each period was always free of reported coronary disease at the start of the period.

Postmenopausal status was defined by responses to the questionnaire. Since young women with a simple hysterectomy and intact ovaries are physiologically similar to premenopausal women, they may have both a reduced risk of coronary disease[13] and a decreased likelihood of receiving estrogen supplements, as compared with women without ovarian function. We therefore attempted to confine the analysis to women with absent ovarian function. We considered a woman postmenopausal (without ovarian function) if she had had a natural or radiation-induced menopause, bilateral oophorectomy, or a hysterectomy without bilateral oophorectomy and had reached the age by which natural menopause had occurred in 90 per cent of the nurses in the cohort — 54 years for current cigarette smokers and 56 for nonsmokers.[14] Although this definition necessarily excluded some women without ovarian function and thus slightly reduced the statistical power of the study, it seemed preferable to the inclusion of women with functioning ovaries.

Incident cases of coronary disease occurring between 1976 and 1978 were related to exposure status as reported on the 1976 questionnaire. All variables except parental history were updated from the 1978 questionnaire, and cases occurring in the period 1978–1980 were related to the exposure status as defined by the 1978 questionnaire.

Analytic Techniques

The primary analysis was based on incidence rates. For all women, person-months were allocated according to the 1976 exposure variables and counted from return of the 1976 questionnaire to death, nonfatal infarction, return of the 1978 questionnaire, or May 31, 1980, whichever came first. For all women completing the 1978 questionnaire, person-months were allocated according to the 1978 exposure variables and counted from the return of the 1978 questionnaire to death, nonfatal infarction, or May 31, 1980, whichever came first.

Since the proportion of subjects completing the follow-up questionnaire was less than 100 per cent (92.7 per cent), we missed the nonfatal events that occurred among the nonrespondents. Therefore, to estimate the incidence of total coronary disease as a first event (fatal plus nonfatal cases), we assumed that the nonrespondents had the same age-specific rates of nonfatal infarction as did the respondents, according to exposure status. The relative risk was defined as the incidence rate in women who had used hormones (estimated as the number of end points divided by person-time of follow-up of hormone users) divided by the rate among women who had never used them.

Age-specific rates for hormone users and nonusers were individually calculated, and age-adjusted relative risks were calculated over five-year age strata.[15] All relative risks presented are age-adjusted. Additional stratified analyses were done to control for the effects of other risk factors. We also performed separate analyses for nonfatal infarction and for fatal events. For all stratified analyses, we calculated the 95 per cent confidence limits that provide a range of plausible values for the relative risk.[16] The significance tests and confidence limits are based on the observed events and do not include the estimated cases. All confidence limits and P values are two-sided. To adjust for multiple potential risk factors simultaneously, proportional-hazards models[17] were developed for "total" coronary disease (including nonfatal myocardial infarction and fatal heart disease) and for nonfatal infarction alone. Proportional-hazards models were not used for fatal coronary disease alone because of the relatively small number of cases.

Results

There were 23,608 postmenopausal women in the study in 1976, with four years of potential follow-up; an additional 8709 became postmenopausal by 1978, with two years of potential follow-up. In 1976, 53 per cent of the postmenopausal women had used hormones at some time, and 35 per cent were current users. Users and nonusers were similar in terms of prevalence of a variety of potential risk factors (Table 1), with the major differences, as might be expected, being type of menopause, past use of oral contraceptives, and degree of obesity (weight divided by the square of height).

Table 1. Distribution of Various Potential Self-Reported Risk Factors According to Postmenopausal Hormone Use among 23,608 Nurses' Health Study Participants.

Variable	Estrogen Use		
	Never	Ever	Current
	per cent of subjects		
Maternal history of myocardial infarction	11.3	11.4	10.9
Paternal history of myocardial infarction	23.0	24.4	24.6
Past oral contraceptive use	17.0	26.3	29.8
Smoking status*			
Never smoked	41.2	39.1	40.8
Former smoker	20.2	23.6	24.2
Current smoker	38.2	36.9	34.5
Hypertension	17.8	18.6	18.1
High serum cholesterol	4.9	6.6	6.2
Diabetes	2.9	2.4	2.1
Bilateral oophorectomy	12.4	53.6	60.3
Quetelet's index (kg/m^2)*			
≤21.2	19.8	23.0	24.0
21.3–24.6	37.5	42.2	43.3
24.6	41.6	33.9	31.8

*Some categories total less than 100 per cent because of missing data and rounding.

The 1976 questionnaires did not include the type or dose of hormone. On the 1978 questionnaire, about 74 per cent of the users indicated that they took conjugated estrogens (in most cases, Premarin), nearly all of which were unopposed by progestins. Of the Premarin users, 35.9 per cent took 1.2 mg per day, 36.3 per cent took 0.6 mg per day, and most of the rest took lower doses.

Among the postmenopausal women who had not had prior coronary disease, there were 65 incident cases of nonfatal myocardial infarction (51 confirmed and 14 probable) and 25 confirmed coronary deaths during 105,786 person-years of follow-up.

Overall, the age-adjusted relative risk for nonfatal infarction plus fatal coronary disease among women who had ever used postmenopausal hormones, as compared with women who never had, was 0.5 (95 per cent confidence limits, 0.3 and 0.8; P = 0.007). The apparent protective effect was largely confined to current users, in whom the relative risk (as compared with women who had never used postmenopausal hormones) was 0.3 (confidence limits, 0.2 and 0.6; P = 0.001) (Table 2). For past users, the relative risk was 0.7 (confidence limits, 0.4 and 1.2; P = 0.17). Of five subjects with sudden death who were not included in the analysis, one was a current hormone user and two were past users.

Adjustment for the risk factors listed in Table 1 in

Table 2. Relative Risk of Total Coronary Disease for Women Who Had Ever Used Postmenopausal Hormones and Current Users, as Compared with Women Who Had Never Used Them.*

	Estrogen Use							
	Never		Ever			Current		
Age	person-years	cases observed	person-years	cases observed	relative risk†	person-years	cases observed	relative risk†
30–34	228.3	0	789.5	0	—	644.4	0	—
35–39	633.1	0	2,170.0	0	—	1,593.9	0	—
40–44	2,073.3	1	5,401.9	2	0.8 (0.1, 4.6)	3,833.0	1	0.6 (0.2, 2.4)
45–49	9,106.9	11	11,064.3	3	0.2 (0.1, 0.7)	6,890.1	2	0.2 (0.1, 0.9)
50–55	34,197.6	40	30,045.8	23	0.6 (0.4, 1.1)	15,239.2	8	0.4 (0.2, 0.9)
56–59	5,238.7	8	4,837.2	2	0.3 (0.1, 1.1)	1,721.4	0	0
Overall age-adjusted	51,477.5	60	54,308.7	30	0.5 (0.3, 0.8)	29,922.0	11	0.3 (0.2, 0.6)

*Total coronary disease includes both nonfatal myocardial infarction and fatal coronary heart disease.

†Calculated relative risks include the number of nonfatal myocardial infarctions estimated to have occurred among the nonrespondents. The overall age-adjusted relative risk was calculated by the maximum-likelihood method. Figures in parentheses are 95 per cent confidence limits. See text for details.

individually stratified analyses did not materially alter the initial findings. In proportional-hazards analysis simultaneous adjustment for a number of potential risk factors (Table 3) also did not alter the simple age-adjusted relative risks. Moreover, there was little apparent modification of the effect in the stratified analyses; the effect was very similar within the different categories of risk factors and within the two follow-up intervals. There was a nonsignificant trend toward decreased protection among women with a positive parental history, but there was no subgroup in which a substantial protective effect could be excluded. There was no appreciable effect of duration of hormone use: among women who had used hormones for up to 36 months, the relative risk for total coronary disease was 0.5, and among those with longer use, it was 0.6. However, the number of cases among hormone users was too small to allow a more detailed examination.

The effect of hormones was similar for different categories of coronary disease. The age-adjusted relative risk in women who had ever used hormones as compared with those who never had was 0.5 (confidence limits, 0.3 and 0.8; P = 0.007) for all nonfatal myocardial infarctions, 0.6 (0.3 and 1.0) for confirmed cases, and 0.3 (0.1 and 0.9) for probable cases. For current users as compared with women who had never used hormones, the age-adjusted relative risk for all nonfatal infarctions was 0.3 (confidence limits, 0.2 and 0.7; P = 0.005). For past users, the relative risk of nonfatal infarction was 0.7 (0.4 and 1.3). Adjustment for other potential risk factors, either individually or simultaneously, did not alter the relative risks of nonfatal myocardial infarction.

A similar pattern emerged for fatal coronary heart disease. As compared with women who had never used hormones, those who had ever used them had an age-adjusted relative risk of 0.6 (confidence limits, 0.3 and 1.3; P = 0.17), and current users had a relative risk of 0.3 (0.1 and 1.2; P = 0.08). Past users had a relative risk of 0.8 (0.3 and 2.0; P = 0.60). These relative risks were not altered by adjustment for other risk factors.

For comparability with other studies, we calculated relative risks for women who had undergone hysterectomy but had an intact ovary. In this group alone, the relative risk for total coronary disease among women who had ever used hormones was 1.3 (0.8 and 2.1; P = 0.37), and among current users it was 1.3 (0.7 and 2.7; P = 0.41). As expected, when these subjects were included in the overall analysis, the apparent hormone effect was attenuated, with a relative risk for total coronary disease of 0.6 (0.4 and 0.8; P = 0.02) among those who had ever used hormones, and 0.5 (0.3 and 0.9; P = 0.01) among current users.

Finally, we conducted an analysis to determine the effect of excluding women with a prior history of coronary disease. As noted above, such women were excluded from the analysis in order to avoid the potential bias due to an influence of the diagnosis on the prescription and use of hormones. However, this restriction has the effect of excluding gradually developing cases diagnosed two years or longer before the onset of an end point. There were eight cases of nonfatal infarction and nine coronary deaths among women with a positive history. Among these cases, there was a slight, nonsignificant trend toward a protective effect. An analysis of the relative risk of total coronary disease in the cohort, without exclusion for prior coronary disease, yielded similar results: 0.6 (0.4 and 0.9;

Table 3. Relative Risks of Coronary Heart Disease, According to Postmenopausal Hormone Use, after Simultaneous Adjustment for Potential Risk Factors in Proportional-Hazards Model.*

Disease and Hormone Use	Coefficient	Relative Risk†	P Value
Total coronary disease			
Current vs. never	−1.22	0.30 (0.14, 0.64)	0.002
Past vs. never	−0.52	0.59 (0.33, 1.06)	0.08
Nonfatal infarction only			
Current vs. never	−1.08	0.34 (0.14, 0.82)	0.02
Past vs. never	−0.43	0.65 (0.33, 1.28)	0.11

*The potential risk factors were a paternal history of infarction (none, at ≤60 yr, at >61 yr), a maternal history of infarction (none, at ≤60 yr, at >61 yr), type of menopause (natural or surgical), time period (1976-1978, 1978-1980), smoking status (current [at three levels of intensity], past, or never), hypertension (yes, no), diabetes (yes, no), past use of oral contraceptives (yes, no), high serum cholesterol level (yes, no), age (five categories), obesity (three categories), current hormone use (yes, no), and past hormone use only (yes, no).

†Figures in parentheses are 95% confidence limits.

P = 0.01) for those who had ever used hormones and 0.4 (0.2 and 0.7; P = 0.002) for current users.

Although our primary focus was on hormone use and the risk of heart disease, we also examined total mortality. There were 379 deaths: 126 among women who had ever used hormones, 48 among those who currently used them, and 253 among those who had never used them. As compared with women who had never used hormones, those who had ever used them had an age-adjusted relative risk for total mortality of 0.5 (0.4 and 0.6) and those who currently used them had a risk of 0.3 (0.2 and 0.4). However, these results are primarily attributable to the large proportion of deaths among participants with cancer at base line, who were not likely to have received estrogens. To eliminate this bias, we then excluded all participants with diagnosed cancer and coronary disease at the base line for each interval. This left 187 total deaths: 88 among women who had ever used hormones, 38 among those who currently used them, and 99 among those who had never used them. As compared with never using postmenopausal hormones, the age-adjusted relative risk of total mortality for some use was 0.9 (0.7 and 1.2; P = 0.42), and that for current use was 0.7 (0.5 and 1.1; P = 0.09).

Discussion

In our data, current hormone users had a reduced rate of coronary disease as compared with women who had never used hormones. The confidence intervals are relatively wide, reflecting uncertainty about the precise magnitude of the apparently large protective effect. Chance is an unlikely explanation for these findings, but possible bias or confounding must be considered. The prospective design greatly reduces the probability of recall or selection bias, which can be serious problems in a case–control study. Incomplete follow-up could distort the findings but only if losses were different for the various subgroups of study subjects. Because the response to follow-up questionnaires was 92.7 per cent, we estimate that only approximately five cases were missed, so even a substantial deviation from the assumption of similar rates of nonfatal infarction for respondents and nonrespondents would be unlikely to alter the results materially. The response rate varied little according to hormone use (92.8 per cent among subjects who had ever used them and 92.5 per cent among those who never had), and there is no reason to believe that its effect would differ between unascertained and observed cases. Follow-up for fatal events was nearly complete (96 per cent).

Some degree of misclassification is likely to have occurred. Information on exposure depended solely on the self-report of the nurse, which may have been inaccurate in some instances. However, misclassification can explain the findings only if it was differential (nonrandom) — for instance, if estrogen use was reported less accurately by women who subsequently had coronary disease. This seems unlikely because of the prospective design of the study and the blinded review of medical records.

We considered the possibility that the apparent protective effect of estrogen could be attributed to some other factor associated with its use. In the stratified and multivariate proportional-hazards analyses, we adjusted for a variety of known and suspected risk factors, based on prospectively gathered data from questionnaires. These analyses showed virtually no confounding. Although the information on these other risk factors was based solely on questionnaires, there are several reasons to support our belief that the self-reports were reliable. First, the subjects in this study were all registered nurses who had demonstrated a particular interest in medical research. Second, in this study, self-reported diabetes, hypertension, and high cholesterol levels were strong predictors of both nonfatal myocardial infarction and fatal coronary heart disease, in agreement with several other studies. Third, in a subgroup of randomly selected nurses reporting hypertension or high cholesterol levels, we validated the conditions by reviewing the hospital or physician records in nearly every instance.[18] Of 161 participants who did not report hypertension, none had a measured blood pressure greater than 160/95 mm Hg, confirming a low rate of false negative reporting.

There is a tendency for leaner women to use hormones more than obese women do (Table 1), which may reflect lower levels of endogenous estrogen[19] and thus more symptoms of deficiency. However, the weak association between thinness and hormone use in our cohort cannot explain the protective effect, since obesity was not a strong independent coronary risk factor in these subjects. Indeed, the apparent protective effect of hormone use was virtually unchanged after adjustment for relative weight.

In the hospital-based case–control studies already reported,[6,20-23] relative risks ranged from 4.2 to 0.6. Hospital-based case–control studies can be difficult to interpret, since hormone use may be associated either directly or inversely with a number of conditions leading to hospitalization, thus complicating the selection of appropriate controls. For example, in one study,[20] 66 per cent of the controls had musculoskeletal disorders or trauma (mostly fractures), which are inversely associated with estrogen use.[24] The use of a sample from the general population as a comparison group tends to avoid these potential difficulties; in such case–control studies, the relative risks have all been less than 1.0.[8,25,26]

There have been eight prospective follow-up studies in which data on hormone use were obtained before the development of coronary disease.[9,27-35] The Lipid Research Clinics study of 2269 women aged 40 to 69 found that hormone use had a significant protective effect on total and cardiovascular mortality, with relative risks of 0.4 and 0.3, respectively.[9,32] In a recently reported study of 7610 women and 435 deaths, the relative risk of fatal myocardial infarction was

0.5 (P = 0.007) among those who had ever used hormones.[34] Only two prospective studies observed relative risks greater than 1.0. In the Framingham study,[29,35] a 50 per cent elevation in risk was observed for total cardiovascular disease (all diagnoses together, including angina) on the basis of only 302 subjects who had ever used hormones. Petitti et al.[30] followed 16,759 women, aged 18 to 54, for an average of 6.5 years. There were 26 infarctions among women who were free of prior coronary heart disease and diabetes, an unknown fraction of whom had functioning ovaries. The relative risk for noncontraceptive estrogen use was 1.2. In summary, it appears that studies of nonfatal myocardial infarction or fatal coronary heart disease (but not those including coronary insufficiency and angina) that have avoided both the inclusion of women with functioning ovaries and the use of hospital controls have consistently observed a protective effect.

One plausible explanation for a protective effect is the favorable influence of estrogens on serum lipid levels. Cross-sectional[36-38] and prospective[3,39,40] studies have demonstrated that estrogens tend to improve the serum lipid profile by lowering low-density-lipoprotein cholesterol and raising the protective[41,42] high-density-lipoprotein cholesterol. However, in the Lipid Research Clinics study, adjustment for lipid levels explained only part of the protective effect,[9] suggesting that other mechanisms may also be involved, perhaps alterations in connective tissue[43,44] or prostaglandins.[45,46] At least part of the effect seems to be short-acting since the benefits were largely limited to current users, and no effect of duration was observed.

The results of this prospective study and other investigations are consistent with the hypothesis that postmenopausal hormone use markedly reduces the risk of coronary heart disease among postmenopausal women. Although we observed no statistically significant reduction in total mortality once women with cancer at base line were eliminated, the proportion of deaths due to confirmed coronary disease was small, and the statistical power to detect an effect was consequently inadequate. A judgment about whether hormones should be routinely prescribed for prophylaxis must be tempered by a consideration of other associated risks and benefits. Estrogens are a well-recognized cause of endometrial cancer.[47-50] Although in most studies the cancers associated with such use tend to be lower in grade and are detected at earlier stages,[49-52] estrogens do cause invasive disease.[49,51,52] In 1984, there were an estimated 39,000 incident cases and 2900 deaths from endometrial cancer.[53] The possible increased risks of breast cancer are a concern, but most studies,[54-56] including the Nurses' Health Study,[57] have shown no effect of hormone use on the overall risk of breast cancer. Some evidence suggests that estrogen use increases the risk of gallbladder disease.[58]

Strong evidence supports the efficacy of exogenous estrogens in treating menopausal symptoms,[59] and the beneficial effect on osteoporosis has been well documented.[24,60-62] In risk–benefit analyses, the benefits of estrogen use for prevention of osteoporosis generally balance or outweigh the risks of endometrial cancer under a range of assumptions,[63,64] without consideration of the effects of coronary disease.

Further work is needed to define the optimal type, dose, and duration of postmenopausal hormone use and to determine whether to add progestogens.[56,65,66] The ethics and feasibility of conducting a clinical trial to obtain more definitive information should be considered carefully.

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