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A Case-Control Study of Myocardial Infarction in Relation to Use of Estrogen Supplements

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Observational epidemiologic studies suggest that the incidence of cardiovascular disease is reduced by about 50% in users of unopposed estrogens, but the reduction may have been overestimated because of a greater tendency for women at lower risk to use estrogens. To minimize bias due to such behavior, the authors conducted a case-control study of first myocardial infarction among Massachusetts women aged 45–69 years during 1986–1990, in which each of 858 cases was age-matched with a control from the same geographic area, and important correlates of estrogen use and myocardial infarction were controlled by conditional logistic regression. The estimated relative risk was 0.9 for ever use of unopposed estrogen (95% confidence interval 0.7–1.2); the estimate decreased with increasing duration of use to 0.6 for 5 or more years of use (p for trend = 0.08). The association with long-term use was stronger for recent use (p for trend < 0.05) than for past use (p for trend = 0.86). There were insufficient data to evaluate estrogens taken together with progestins. The results suggest that unopposed estrogen use may reduce the risk of first myocardial infarction, that the reduction is related to the duration and recency of use, and that it may be smaller than previously believed. Despite efforts to control confounding, observational studies cannot rule out the possibility that a tendency for women at lower risk for myocardial infarction to use estrogens has contributed to the reduced risk in estrogen users, and randomized trials are needed. *Am J Epidemiol* 1993;137:54–63.

estrogen replacement therapy; myocardial infarction

Many observational studies (1–10), most recently a large follow-up study of American nurses (11), suggest that the postmenopausal use of unopposed estrogens confers protection against cardiovascular disease; it has been estimated that the risk in women who have ever taken estrogens is reduced by about one-half (2). It is possible that a protective effect has been overestimated because women at reduced risk of cardiovascular

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Abbreviations: CI, confidence interval; RR, relative risk.

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disease may be more likely to use estrogens (11–14). We assessed the relation of the risk of first myocardial infarction to estrogen use in a case-control study designed with the aim of minimizing bias arising from the selective use of estrogen by women at reduced risk. To control, at least in part, for confounding due to health behaviors, we matched each case with a control woman of similar age from the same geographic area, and we controlled important correlates of estrogen use and myocardial infarction in the analysis.

MATERIALS AND METHODS

Data collection

The data were collected during 1986–1990 from women who were 45–69 years of age and lived in Massachusetts.

Potential cases of first myocardial infarction were identified by weekly telephone calls to the coronary care units of 52 hospitals. The doctors were contacted for details of the diagnosis, permission to approach the patient, and the patient's telephone number if it was unlisted; 94 percent of the doctors gave permission, and of the patients who were then contacted, 90 percent participated.

Massachusetts cities and towns are divided into precincts; within a city or town, each precinct contains approximately the same number of people. A typical precinct in Massachusetts might include some 2,500 people. We matched each case with a control woman from the same precinct who was in the same 5-year age group and who had no history of myocardial infarction. The controls were selected in a standard manner from Massachusetts town books. The books list the name, address, age, and sex of each adult resident and are satisfactorily complete: of the first 150 cases, 88 percent were correctly listed at the addresses given by their physicians. Only women who had published telephone numbers (73 percent) were included as controls; we failed to reach 3 percent; of those contacted, 83 percent participated.

A standard questionnaire was administered by nurse-interviewers to the cases and controls. For 27 percent of the cases, the interview was in person; for the remainder, and for all controls, the interview was by telephone. Information was obtained on demographic factors, history of conditions which predispose to myocardial infarction (such as history of diabetes or elevated cholesterol level), family history of myocardial infarction, exercise, cigarette smoking, alcohol use, and use of selected drugs, including noncontraceptive estrogens and progestins. For each drug used, the name, the indication, the date started, and the frequency and duration of use were recorded. For estrogen and progestogen supplements, the doses were also recorded.

We interviewed 911 potential cases and obtained the discharge summaries of 98 percent: 6 percent did not meet the World Health Organization criteria for the diagnosis of myocardial infarction (15) (pathologic Q waves with evolution, or elevated cardiac enzymes together with typical history of chest pain or electrocardiographic evidence of ST-T wave evolution), or they had a history of rheumatic valvular disease, cardiomyopathy, or cardiac surgery. The remaining 858 women constituted the final case series: the median age was 60 years and 98 percent were white. Among the 858 matched controls, the median age was 60 years and 97 percent were white.

Analysis

Women were considered to be postmenopausal if menses had ceased because of removal of the uterus or both ovaries or, for women with an intact uterus, if menses had ceased for at least one year. Women who had taken an estrogen or a progestin orally for replacement in the perimenopausal period or postmenopausally, and whose use had lasted for at least a month, were classified as users of estrogen alone, progestin alone, or estrogen with progestin (combination therapy). Women whose use had lasted for less than a month were considered to be

nonusers. There were six cases and 10 controls who had taken both estrogen and progestin for at least a month but not concomitantly, or had taken estrogen or progestogen injections for at least a month; they were placed in a separate category.

Relative risk estimates (i.e., odds ratios) for categories of estrogen and progestin use, relative to no use of either drug, were estimated by conditional logistic regression (16), which controlled for the matching factors, age and precinct, as well as for multiple confounding factors. Among the controls, the use of unopposed estrogens was associated with certain indicators of increased risk of myocardial infarction, most notably with older age and early menopause, and also with heavy smoking and positive histories of myocardial infarction in a parent or sibling, drug-treated hypertension, drug-treated angina pectoris, elevated serum cholesterol, and drug-treated diabetes mellitus (table 1). (The latter four conditions may be related to estrogen use, in part, because women who seek medical care tend both to take estrogens and to have their medical conditions diagnosed.) Use was also associated with several factors which indicate a reduced risk (table 1): leanness, participation in vigorous exercise, greater years of education, alcohol use, and use of medical care. Thus, it was necessary to control these and other potential confounding factors in the analysis. Terms were included in the logistic regression for histories of drug-treated hypertension, drug-treated diabetes mellitus, drug-treated angina pectoris, elevated serum cholesterol, and myocardial infarction before age 60 years in a parent or sibling, and for age at and type of menopause (premenopausal/hysterectomy with retention of one or both ovaries/menopause due to natural causes or bilateral oophorectomy before age 45 years/menopause due to natural causes or bilateral oophorectomy at ages 45–49 years/menopause due to natural causes or bilateral oophorectomy at age 50 years or older), cigarette smoking (<25/≥25 per day), alcohol consumption (<1/≥1 drink per week), coffee consumption (<5/≥5 cups per day), body mass index (kg/m^2) (<24/24–28/≥29), Framingham type A behavior score (17) (<7/7–10), vigorous physical activity (e.g., running, biking) (<1/≥1 hour per week), years of education (<13/≥13), and number of visits to a physician in the previous year (0/1–9/≥10). The most important factor in terms of the impact on the unadjusted relative risk estimate was age at and type of menopause. Allowance for additional factors, one at a time, resulted in small changes in the estimate (e.g., control for vigorous physical activity moved it toward the null, while control for cigarette smoking had the opposite effect). However, allowance for the additional factors together resulted in little change in the relative risk after age at and type of menopause was controlled. A term for total months of estrogen use was used to test for trend in the relative risk estimate across duration of use.

Because estrogen use may influence the risk of myocardial infarction via an effect on serum lipids (18), it could be argued that history of elevated serum cholesterol should not be controlled. However, inclusion of this variable in the logistic regression slightly strengthened the inverse association of estrogen use with risk of myocardial infarction; also, in another study in which control for high density lipoprotein resulted in a considerable weakening in the apparent protective effect, control for total cholesterol had no effect (6).

A subanalysis was conducted in which cases interviewed in person were excluded, along with their matched controls: the results were similar to those given below for the entire study population. Results were also little changed when cases with unlisted telephone numbers, along with their matched controls, were excluded.

RESULTS

Use of replacement therapy is shown in table 2. Twenty-one percent of both the cases and controls had used unopposed estrogens, most commonly conjugated estrogens, with a mean duration of use of 52 months in cases and 57 months in controls. The multivariate relative risk estimate for

TABLE 1. Unopposed estrogen use for ≥5 years among 858 community controls in a Massachusetts case-control study conducted 1986–1990, according to selected factors

Factor	No.	≥5 years of use* (%)
All controls	858	6
Age (years)		
45–54	202	4
55–64	417	7
65–69	239	8
Cigarette smoking (no./day)		
None	638	6
<25	150	6
≥25	67	8
History of		
Drug-treated hypertension	273	8
Drug-treated angina pectoris	44	16
Drug-treated diabetes mellitus	30	7
Elevated cholesterol	179	8
Family history of myocardial infarction	138	8
Body mass index (kg/m^2)		
<24	330	8
24–28	327	6
≥29	199	5
Framingham type A behavior score		
<4.3	542	5
4.3–<7	220	8
7–10	79	8
Vigorous exercise (hour/week)		
≥1	145	10
<1	658	6
Years of education		
<12	131	6
12	371	5
≥13	355	8
Alcohol use (drink/week)		
≥1	325	8
<1	357	5
Age (years) at menopause†		
<45	154	14
45–49	180	4
≥50	324	4
Menopausal status		
Premenopausal	102	0
Natural menopause	519	3
Hysterectomy with retention of ≥1 ovary	96	12
Bilateral oophorectomy	140	20
Visits to a physician in previous year		
0	158	2
≥1	693	7

* Total duration of ever use.
† Due to natural causes or bilateral oophorectomy.

ever use of unopposed estrogens was 0.9 (95 percent confidence interval (CI) 0.7–1.2). The estimates for use of progestin alone (cases, 0.7 percent; controls, 0.8 percent) and for combination therapy (cases, 2.7 percent; controls, 3.5 percent) were 1.3 and 1.2, respectively, and both estimates were compatible with 1.0. Among the users of combination therapy, there were 11 cases and seven controls who had used estrogens for 5 or

TABLE 2. Estrogen and progestin use among 858 cases of myocardial infarction and 858 matched community controls in a Massachusetts case-control study conducted 1986–1990*

Use of estrogen or progestin	No. of cases	No. of controls	Multivariate relative risk estimate†	95% confidence interval
No use of estrogen or progestin	647	635	1.0‡	
Unopposed estrogen	176	176	0.9	0.7–1.2
Estrogen together with progestin	23	30	1.2	0.6–2.4
Progestin only	6	7	1.3	0.4–4.9

* Six cases and 10 controls who used both estrogen and progestin but not concomitantly or who took estrogen or progestin injections are excluded from the table.

† Allowance was made for age, precinct, histories of hypertension, diabetes mellitus, angina pectoris, elevated serum cholesterol, and myocardial infarction before age 60 years in a parent or sibling, and for age at and type of menopause, cigarette smoking, alcohol consumption, coffee consumption, body mass index, Framingham type A behavior score, vigorous physical activity, years of education, and number of visits to a physician in the previous year.

‡ Reference category.

TABLE 3. Unopposed estrogen use among 858 cases of myocardial infarction and 858 matched community controls in a Massachusetts case-control study conducted 1986–1990, according to the duration of use

	No. of cases	No. of controls	Multivariate relative risk estimate	95% confidence interval
No use of estrogen or progestin	647	635	1.0†	
Duration of estrogen use (years)				
<1	56	53	0.9	0.6–1.5
1–2	45	46	1.1	0.6–2.0
3–4	16	18	0.8	0.3–1.9
5–9	21	24	0.6	0.3–1.3
10–14	13	10	1.0	0.4–2.9
≥15	14	20	0.4	0.2–1.0
Unknown	11	5	–	

* Allowance was made for age, precinct, histories of hypertension, diabetes mellitus, angina pectoris, elevated serum cholesteol, and myocardial infarction before age 60 years in a parent or sibling, and for age at and type of menopause, cigarette smoking, alcohol consumption, coffee consumption, body mass index, Framingham type A behavior score, vigorous physical activity, years of education, and number of visits to a physician in the previous year.

† Reference category.

more years, yielding a multivariate relative risk estimate of 2.6 (95 percent CI 0.8–8.4); the corresponding estimate for use of less than 5 years duration was 0.5 (95 percent CI 0.2–1.5). Further consideration is confined to the use of unopposed estrogens.

Sixty-two percent of case users and 67 percent of control users had taken unopposed estrogens for at least 1 year (table 3). The multivariate relative risk estimate decreased, although not consistently, as the duration of use increased (z for trend = −1.78, $p = 0.08$). For 5 or more years of use (long-term use), the estimate was 0.6 (95 percent CI 0.4–1.1).

Data according to both duration and recency of use are shown in table 4. For recent use (in the previous year), the overall multivariate relative risk estimate was 0.8 (95 percent CI 0.4–1.3); the corresponding estimate for past use was 0.9 (95 percent CI 0.7–1.3). The estimate for 5 or more years of use was more reduced in recent users (relative risk (RR) = 0.5, 95 percent CI 0.3–1.1) than in past users (RR = 0.8, 95 percent CI 0.3–1.7), but the difference was not statistically significant. A trend for the multivariate relative risk estimate to decrease as the duration of use increased was statistically significant in recent users (z for trend = −1.98, $p < 0.05$), but not in past users (z for trend = −0.18, $p = 0.86$).

TABLE 4. Unopposed estrogen use among 858 cases of myocardial infarction and 858 matched community controls in a Massachusetts case-control study conducted 1986–1990, according to the duration and recency of use

	Recency of estrogen use							
	Recent*				Past			
	No. of cases	No. of controls	Multivariate relative risk estimate†	95% confidence interval	No. of cases	No. of controls	Multivariate relative risk estimate*	95% confidence interval
Total	45	49	0.8	0.4–1.3	131	127	0.9	0.7–1.3
Duration of estrogen use (years)								
<1	5	4	1.5	0.3–8.0	51	49	0.9	0.5–1.5
1–4	10	11	1.2	0.4–3.7	51	53	1.0	0.6–1.7
5–9	8	11	0.6	0.2–2.0	13	13	0.7	0.3–1.7
≥10	18	22	0.5	0.2–1.1	9	8	1.0	0.3–3.6
Unknown	4	1	–		7	4	–	

* Use within the previous year.

† The reference category for the relative risk estimates comprises 647 cases and 635 controls who did not use estrogen or progestin; allowance was made for age, precinct, histories of hypertension, diabetes mellitus, angina pectoris, elevated serum cholesterol, and myocardial infarction before age 60 years in a parent or sibling, and for age at and type of menopause, cigarette smoking, alcohol consumption, coffee consumption, body mass index, Framingham type A behavior score, vigorous physical activity, years of education, and number of visits to a physician in the previous year.

In table 5, the data for long-term use are presented according to body mass index, age, type of menopause, age at menopause, smoking status, and dose of estrogen. The multivariate relative risk estimate was reduced in all categories except among the leanest women (RR = 1.2) and smokers of 1–24 cigarettes per day (RR = 1.0). None of the relative risk estimates, except that in the heaviest women (RR = 0.2), was statistically significant. There were insufficient data to estimate the relative risk in women under 50 years of age.

DISCUSSION

In the present study, women who had ever used unopposed estrogens were estimated to have a risk of first myocardial infarction similar to that of women who had never used them: the multivariate relative risk estimate was 0.9. However, the risk decreased as the duration of use increased ($p = 0.08$), and use for 5 or more years was associated with an estimated reduction of 40 percent. The trend for the relative risk to decrease with increasing duration of use was statistically significant in recent users but not in past users. The reduced risk for long-term users was evident in all categories of menopausal status, in smokers and nonsmokers, and in those who used higher and lower doses of conjugated estrogens. There was not a reduction in the leanest women. Many subgroups were assessed, however, and the lack of an effect in lean women could be due to chance.

We could not evaluate whether an effect of unopposed estrogens differs for fatal and nonfatal disease because the present study only included survivors. Other studies suggest that the effect of estrogen on fatal outcomes is similar to that on nonfatal outcomes (1–11).

Many previous studies have suggested a protective effect of unopposed estrogens against ischemic heart disease (1–11). Among the follow-up studies, the Lipid Research Clinic study (5, 6) reported a 63 percent reduction in cardiovascular mortality among estrogen users; the protective effect appeared to be mediated, in part, through increased levels of high density lipoprotein (6). In the same study, all-cause mortality was reduced by 46 percent. There were no data on the duration of use. In the Nurses' Health Study (7, 8, 11), the risk of major coronary disease was reduced more in recent estrogen users, by about 45 percent, than in past users, 17 percent; the effect was not

TABLE 5. Unopposed estrogen use for ≥5 years among 858 cases of myocardial infarction and 858 matched community controls in a Massachusetts case-control study conducted 1986–1990, according to age, type of menopause, age at menopause, cigarette smoking, body mass index, and estrogen dose

Factor		No use of estrogen or progestogen	≥5 years of use	Multivariate relative risk estimate*	95% confidence interval
Age (years)					
45–49	Cases	72	4	–	
	Controls	74	1		
50–59	Cases	228	18	0.8	0.3–1.8
	Controls	228	19		
60–69	Cases	347	26	0.5	0.3–1.1
	Controls	333	34		
Type of menopause					
Natural	Cases	451	11	0.7	0.3–1.9
	Controls	422	14		
Hysterectomy with retention of ≥1 ovary	Cases	57	9	0.6	0.2–2.0
	Controls	58	12		
Bilateral oophorectomy	Cases	77	28	0.7	0.3–1.5
	Controls	61	28		
Age (years) at menopause†					
<45	Cases	158	26	0.7	0.3–1.5
	Controls	101	21		
45–49	Cases	156	7	0.7	0.2–2.3
	Controls	136	8		
≥50	Cases	212	6	0.6	0.2–1.8
	Controls	247	13		
Cigarettes per day					
None	Cases	285	19	0.5	0.3–1.1
	Controls	470	39		
<25	Cases	187	14	1.0	0.3–2.7
	Controls	116	10		
≥25	Cases	174	15	0.5	0.1–1.6
	Controls	49	5		
Body mass index (kg/m^2)					
<24	Cases	203	27	1.2	0.6–2.3
	Controls	237	25		
24–28	Cases	222	16	0.4	0.2–1.1
	Controls	246	20		
≥29	Cases	220	5	0.2	0.04–0.7
	Controls	150	9		
Estrogen dose (mg)					
≤0.625	Cases	647	17	0.6	0.3–1.5
	Controls	635	18		
>0.625	Cases	647	10	0.6	0.2–1.7
	Controls	635	12		

* Reference category is nonusers within each category; within each stratum, allowance was made for age, precinct, histories of hypertension, diabetes mellitus, angina pectoris, elevated serum cholesterol, and myocardial infarction before age 60 years in a parent or sibling, and for age at and type of menopause, cigarette smoking, alcohol consumption, coffee consumption, body mass index, Framingham type A behavior score, vigorous physical activity, years of education, and number of visits to a physician in the previous year, with the exception of the stratifying factor itself.

† Among women with menopause due to natural causes or bilateral oophorectomy.

influenced by the duration of use (11). In that study, among ever users of estrogens, cardiovascular mortality was reduced by 28 percent and all-cause mortality by 11 percent. In the Leisure World study of elderly women (10), in which arteriosclerotic and cerebrovascular mortality was reduced in estrogen users, the effect was strongly related to both the duration and recency of use. Among women who had used estrogens for

15 or more years and who were current users at the start of follow-up, there was a 40 percent reduction in overall mortality, mostly due to substantially decreased mortality from cardiovascular disease but also due to a smaller reduction in cancer mortality.

One follow-up study, the Framingham Study, showed an adverse effect of estrogen: there was a 90 percent increase in coronary heart disease incidence and more than a doubling in cerebrovascular disease incidence in estrogen users (19). However, a reanalysis suggested protection in women under age 60 years and an increased risk in older women, although neither finding was statistically significant (20).

Two earlier case-control studies by the present investigators showed no association of estrogen use with risk of myocardial infarction (21, 22). In both studies, however, statistical power to detect an effect was limited, and in one of them the women were all under age 50 years (22).

In the present study, we observed little, if any, effect of "ever" use of estrogens, a finding at variance with the 50 percent reduction in risk that has been estimated (2). However, the indication by our data that the reduction is influenced by the duration of use accords with the Leisure World findings (10), and the indication of a stronger effect in recent users accords with both the Leisure World (10) and Nurses' Health Study results (11).

A limitation to all the studies conducted to date is the possibility of overestimation of a protective effect, resulting from a tendency for women at low baseline risk of cardiovascular disease to use estrogens (11–14). The findings from the Coronary Drug Project, a clinical trial in which men with first myocardial infarctions were randomized to clofibrate or placebo, suggest that such a bias may be large and may not be amenable to "correction" in the analysis (23). In the trial, there was no overall difference in mortality between the clofibrate and placebo groups (20 percent vs. 21 percent). However, the mortality of good adherers to clofibrate was substantially and significantly lower, by 40 percent, than that of poor adherers (15 percent vs. 25 percent), perhaps suggesting a beneficial effect of clofibrate. Yet, among men randomized to placebo, mortality was also substantially and significantly reduced in good adherers, by 46 percent (15 percent vs. 28 percent). Adjustment for 40 baseline characteristics did not materially diminish the differences. Thus, adherers to prophylactic drug use may differ appreciably from nonadherers in predictors of risk that are difficult to specify and measure and, therefore, to take into account. Possibly this is also the case for users and nonusers of supplemental estrogens.

Further evidence of selective use of estrogens is provided by the Walnut Creek contraceptive follow-up study: estrogen users were at reduced risk not only of cardiovascular disease, but of accidents and homicides as well (12). In the three follow-up studies cited above (5, 6, 10, 11), mortality not only from cardiovascular disease but from other causes as well was reduced in estrogen users, possibly reflecting such selective use. (On the other hand, it may indicate that estrogen use has a favorable impact on several different biologic systems.)

In the present study, we attempted to minimize bias due to the selective tendency of healthier women to use estrogens by age-matching each case with a control from the same geographic area. Because women with similar socioeconomic backgrounds are more likely to have similar health behaviors, we reasoned that such matching would serve to control factors, particularly "life-style" factors, which are difficult to measure or quantify but which may be related both to estrogen use and to the risk of myocardial infarction. In addition, specific measured factors, some related to an increased and some to a decreased risk, were controlled in the analysis. Because some factors, such as a history of elevated cholesterol or of adult onset diabetes, are reported with imprecision, control was necessarily incomplete.

It is possible that the lesser reduction in risk associated with estrogen use in our study compared with previous studies is explained by fuller control of confounding. Whether this is indeed the case will only be established

when the results of well-conducted randomized controlled trials of estrogen use become available. Another possible explanation for the smaller estimate of protection in the present study—that cases reported estrogen use more completely than controls—is unlikely because validation studies suggest that long-term estrogen use is recalled reasonably well (24).

In recent years, there has been a trend to use of estrogens together with a progestin (25). One rationale is that the addition of a progestin protects against endometrial cancer (1). However, it has been recommended that this regimen also be used by women who have had hysterectomies (26). Progestins may reverse the beneficial effect of unopposed estrogens on serum lipids (1, 27–31) and perhaps also adversely affect glucose tolerance and thrombogenesis (31–33); this could lead to an increased risk of cardiovascular disease. Our sparse data on combination therapy are not informative, and we know of no informative data from other studies. There remains a need to evaluate the cardiovascular impact of this regimen.

REFERENCES

1. Ernster VL, Bush TL, Huggins GR, et al. Benefits and risks of menopausal estrogen and/or progestin hormone use. Prev Med 1988;17:201–23.
2. Stampfer MJ, Colditz GA. Estrogen replacement therapy and coronary heart disease: a quantitative assessment of the epidemiologic evidence. Prev Med 1991;20:47–63.
3. Pfeffer RI, Whipple GH, Kurosaki TT, et al. Coronary risk and estrogen use in postmenopausal women. Am J Epidemiol 1978;107:479–87.
4. Ross RK, Paganini-Hill A, Mack TM, et al. Menopausal estrogen therapy and protection from death from ischaemic heart disease. Lancet 1981;1: 858–60.
5. Bush TL, Cowan LD, Barrett-Connor E, et al. Estrogen use and all-cause mortality. Preliminary results from the Lipid Research Clinics Program Follow-Up Study. JAMA 1983;249:903–6.
6. Bush TL, Barrett-Connor E, Cowan LD, et al. Cardiovascular mortality and noncontraceptive use of estrogen in women: results from the Lipid Research Clinic Program Follow-up Study. Circulation 1987;75:1102–9.
7. Stampfer MJ, Willett WC, Colditz GA, et al. A prospective study of postmenopausal estrogen therapy and coronary heart disease. N Engl J Med 1985;313:1044–9.
8. Colditz GA, Willett WC, Stampfer M, et al. Menopause and risk of coronary heart disease in women. N Engl J Med 1987;316:1105–10.
9. Criqui MH, Suarez L, Barrett-Connor E, et al. Postmenopausal estrogen use and mortality: results from a prospective study in a defined, homogeneous community. Am J Epidemiol 1988;128: 606–14.
10. Henderson BE, Paganini-Hill A, Ross RK. Decreased mortality in users of estrogen replacement therapy. Arch Intern Med 1991;151:75–8.
11. Stampfer MJ, Colditz GA, Willett WC, et al. Postmenopausal estrogen therapy and cardiovascular disease. Ten-year follow-up from the Nurses' Health Study. N Engl J Med 1991;325:756–62.
12. Petitti DB, Perlman JA, Sidney S. Postmenopausal estrogen use and heart disease. N Engl J Med 1986; 315:131–2.
13. Harris RB, Laws A, Reddy VM, et al. Are women using postmenopausal estrogens? A community survey. Am J Public Health 1990;80:1266–8.
14. Cauley JA, Cummings SR, Black DM, et al. Prevalence and determinants of estrogen replacement therapy in elderly women. Am J Obstet Gynecol 1990;163:1438–44.
15. Ischemic Heart Disease Registers. Report of the Fifth Working Group. Copenhagen: World Health Organization, 1971.
16. Breslow NE, Day NE, Halvorsen KT, et al. Estimation of multiple relative risk functions in matched case-control studies. Am J Epidemiol 1978;108:299–307.
17. Haynes SG, Levine S, Scotch N, et al. The relationship of psychosocial factors to coronary heart disease in the Framingham Study. I. Methods and risk factors. Am J Epidemiol 1978;107:362–83.
18. Bush T, Miller V. Effects of pharmacologic agents used during menopause: Impact on lipids and lipoproteins. In: Mishell DR Jr, ed. Menopause: physiology and pharmacology. Chicago: Year Book Medical Publications, 1987:121–36.
19. Wilson PWF, Garrison RJ, Castelli WP. Postmenopausal estrogen use, cigarette smoking, and cardiovascular morbidity in women over 50, The Framingham Study. N Engl J Med 1985;313:1038–43.
20. Eaker ED, Castelli WP. Coronary heart disease and its risk factors among women in the Framingham study. In: Eaker E, Packard B, Wenger NK, et al, eds. Coronary heart disease in women: proceedings of an NIH workshop. New York: Haymarket Doyman Inc, 1987:122–32.
21. Rosenberg L, Armstrong B, Jick H. Myocardial infarction and estrogen therapy in postmenopausal women. N Engl J Med 1976;294:1256–9.
22. Rosenberg L, Slone D, Shapiro S, et al. Noncontraceptive estrogens and myocardial infarction in young women. JAMA 1980;244:339–42.
23. The Coronary Drug Project Research Group. Influence of adherence to treatment and response of cholesterol on mortality in the Coronary Drug Project. N Engl J Med 1980;303:1038–41.
24. Goodman MC, Nomura AMY, Wilkens LR, et al. Agreement between interview information and physician records on history of menopausal estrogen use. Am J Epidemiol 1990;131:815–25.
25. Hemminki E, Kennedy DL, Baum C, et al. Prescribing of noncontraceptive estrogens and progestins in the United States, 1974–86. Am J Public Health 1988;78:1479–81.

26. Gambrell RD Jr. Proposal to decrease risk and improve prognosis of breast cancer. Am J Obstet Gynecol 1984;150:119–32.
27. Ottosson UB, Johansson GB, von Schoultz B. Subfractions of high-density lipoprotein cholesterol during estrogen replacement therapy: a comparison between progestogens and natural progesterone. Am J Obstet Gynecol 1985;151:746–50.
28. Hirvonen E, Mölkönen M, Manninen V. Effects of different progestogens on lipoproteins during postmenopausal replacement therapy. N Engl J Med 1981;304:560–3.
29. Christiansen C, Christiansen MS, Grande P, et al. Low-risk lipoprotein pattern in postmenopausal women on sequential oestrogen/progestogen treatment. Maturitas 1984;5:193–9.
30. Jensen J, Nilas L, Christiansen C. Cyclic changes in serum cholesterol and lipoproteins following different doses of combined postmenopausal hormone replacement therapy. Br J Obstet Gynaecol 1986;93:613–18.
31. Godsland IF, Crook D, Simpson R, et al. The effects of different formulations of oral contraceptive agents on lipid and carbohydrate metabolism. N Engl J Med 1990;323:1375–81.
32. Oral contraceptives, venous thrombosis and varicose veins: Royal College of General Practitioners' Oral Contraceptive Study. J R Coll Gen Pract 1978; 28:393–9.
33. Alkjaersig N, Fletcher A, Burstein R. Association between oral contraceptive use and thromboembolism: a new approach to its investigation based on plasma fibrinogen chromatography. Am J Obstet Gynecol 1975;122:199–211.