MENOPAUSAL OESTROGEN THERAPY AND PROTECTION FROM DEATH FROM ISCHAEMIC HEART DISEASE

RONALD K. ROSS   ANNLIA PAGANINI-HILL
THOMAS M. MACK   MARY ARTHUR
          BRIAN E. HENDERSON

Department of Family and Preventive Medicine, University of Southern California School of Medicine, Los Angeles, California, U.S.A.

Summary   The medical records of a Los Angeles retirement community were examined to find out the association between oestrogen replacement therapy and death from ischaemic heart disease. Women dying from ischaemic heart disease over a five-year period were compared with living and deceased control groups; both controls were matched with cases for date of birth, date of entry into the community, race, and socioeconomic status. The deceased control was also matched for date of death. Compared with living controls cases using conjugated oestrogens had a risk ratio for death from ischaemic heart disease of 0·43 (95% confidence interval 0·24–0·75). Comparison with deceased controls gave a similar relative risk. This association was not due to identifiable confounding factors. Other risk factors for ischaemic heart disease, including hypertension, diabetes, stroke, angina pectoris, and heavy cigarette smoking, were confirmed by this study.

Introduction

UNTIL recently oestrogen replacement therapy in the menopause was widely thought to decrease the risk of coronary artery disease. This belief rested on the low rate of coronary artery disease in premenopausal women compared with men of similar age, and on the apparent increased risk of coronary artery disease associated with an early natural or surgical menopause.[1-3] Several observations have cast doubt on the basis for this hypothesis. Age-specific mortality rates from coronary artery disease in women show no change in the rate of age-specific increase during the perimenopausal period.[4] Furthermore, in a randomised trial among men who had had previous myocardial infarction, high-dose oestrogen therapy had to be discontinued because of an excess of subsequent infarctions in the treated group.[5] Moreover, hyperoestrogenism may be an important risk factor for myocardial infarction in young men.[6] Finally, oral contraceptives increase the risk of myocardial infarction in young women, especially in those who smoke.[7]

In the past 5 years, two case-control studies have studied the association of menopausal oestrogen use with coronary artery disease. Rosenberg et al. studied current oestrogen use in 328 cases of non-fatal myocardial infarction and 6730 hospital controls.[8] The crude risk ratio was 0·39 for current oestrogen use in women over 50. However, most of the observed protective effect disappeared after adjusting for other risk factors for myocardial infarction, even though only 5 of 321 cases (1·6%) in this age category were current users of the drug. Pfeffer et al. studied incident myocardial infarctions during an 11-year period among female residents of a retirement community.[9] The crude risk ratio for ever-use of oestrogen replacement therapy as determined from pharmacy records was 0·86, the small protective effect again being largely explained by other risk factors for myocardial infarction. When we studied various risks and benefits of oestrogen replacement in the same retirement community[10,11] we found

that pharmacy records did not tally with medical records; over one-third of women who had oestrogen usage noted on their medical records at the community medical centre did not have records of oestrogen prescriptions in the pharmacy records. It is also possible that women with disabilities from coronary artery disease or its risk factors may be more likely to use the pharmacy in the medical centre than would women without such increased risk. We have found a good correspondence between oestrogen use as recorded on medical records and that obtained by personal interview, especially for long-term use.[10,11] For these reasons, we decided to study the association between oestrogen replacement therapy and death from coronary artery disease by using medical records as the data source for evidence of past oestrogen usage.

Patients and Methods

The retirement community opened in 1962 near Los Angeles County and at the time of study contained about 20 000 residents. The residents are almost uniformly White, highly educated, and financially well-to-do. Administrators of the community estimate that 85% of the residents use the affiliated medical centre as their principal source of medical care. The overall frequency of oestrogen use in the women is high.[10,11]

Since 1971, we have routinely collected the death certificates of all those who died while staying in the community. We code all primary or underlying causes of death according to the International Classification of Disease (I.C.D.), 8th revision.[12] All females whose primary or underlying cause of death was ischaemic heart disease (IHD) (I.C.D., 8th revision, codes 410–414) were selected for this study providing that the woman died between 1971 and 1975 inclusive and was under 80 years of age at death. There were 146 such individuals. 13 of them had never used the medical centre and were excluded. The mean age at death of the qualifying cases was 73.

For each case, a living control matched by race, birthdate (±1 year), and date of entry into the community (±1 year) was selected by sequentially searching a complete 1976 register of residents. In order to avoid any bias resulting from the extra medical attention that the cases may have received towards the end of their lives, a second control was chosen from the register of all those who died in 1971–76. The deceased control was additionally matched on date of death (±2 years). We excluded women whose cause of death was known or suspected to be oestrogen related: cancer of the breast, ovary, and endometrium, fracture-related condition, cerebrovascular disease, and other diseases of the arteries, arterioles, and capillaries. We were able to obtain a living control for each case and a deceased control for 124 of the 133 study cases. 70 of the deceased controls had died from neoplasia, 12 from diseases of the respiratory system, 12 from injury-related causes, 9 from diseases of the digestive system, and 21 from miscellaneous causes. As with cases, controls were excluded if they had not used the medical centre during their stay in the community. We replaced 21 controls from the living control group and 7 from the deceased control group for this reason.

Medical records were reviewed by an experienced medical record abstractor. For each control the recorded medical history was presumed to end at the date of death of the case and no information from subsequent records was abstracted.

Relative risk estimates were computed with the use of the linear logistic model applied to individually matched case-control studies.[13] Each pair consisting of a case and her matched control was considered as a single stratum, thus preserving the individual matching in the calculation of relative risks. Confounding and effect modification were examined both by stratification and by entering single terms for the potential confounding and effect modifying variables into the logistic model. All reported p-values are based on two-tailed likelihood ratio χ^2 tests.

Results

Most well-known risk factors for ischaemic heart disease, including history of stroke, hypertension, angina pectoris, and previous myocardial infarction, were strong and statistically significant risk factors for death from IHD whether the comparison was with the matched living or the matched deceased controls (see accompanying table). Diabetes before age 65 was also a strong and consistent risk factor ($p = 0.12$ and $p = 0.10$, when cases were compared with the living and deceased control groups, respectively).

Cigarette smoking per se was not a strong risk factor when either control group was used for comparison, but for those persons for whom we had detailed smoking histories, cigarette smoking in excess of one pack per day carried a high risk ($RR = 3.3$) compared with the living controls. Among those who gave a detailed history of alcohol intake, women who had drunk alcohol in moderation (fewer than two drinks per day) had a reduced risk of death from IHD, compared with the living controls. There was no relation between risk of dying of IHD and height, weight, Quetelet's index (weight/height^2), or a history of gout or gallbladder disease.

The ingestion of drugs used in the treatment of diseases associated with IHD were risk factors for death from IHD. There was a significant risk of IHD associated with the use of several types of antihypertensive agents (reserpine, thiazide, and "other antihypertensives"), hypoglycaemic drugs, and cardiovascular preparations (table). The ingestion of conjugated oestrogens, which were by far the most commonly used type of oral oestrogens, reduced risk ratios substantially and significantly.

In women with no history of either previous myocardial infarction, stroke, angina pectoris, diabetes, or hypertension, the preventive effect of oestrogen use was even more apparent ($RR_{living} = 0.43$; $RR_{deceased} = 0.39$) than when a history of one or more of these risk factors was present ($RR_{living} = 0.48$; $RR_{deceased} = 0.58$).

Because of the reported synergistic effect of oral contraceptive use and cigarette smoking on risk of myocardial infarction,[7] the risk ratio for conjugated oestrogen use in heavy cigarette smokers was of particular interest. When living controls were used for comparison the risk ratio in women currently smoking one pack of cigarettes or more per day was 0.80, and that for women who were not currently smoking or who smoked less than a pack of cigarettes per day was 0.58. The number of cigarettes smoked per day was unknown in 17% of cases and in 15% of controls.

In case the clinical diagnosis of IHD as expressed on death certificates might have been inaccurate, we compared the risk for necropsy-confirmed cases ($n = 46$) with that of their matched controls. Conjugated oestrogen use gave similar protection to necropsy-confirmed cases ($RR_{Living} = 0.39$, $RR_{Deceased} = 0.55$) as to non-necropsy-confirmed cases ($RR_{Living} = 0.45$, $RR_{Deceased} = 0.58$).

Since many women had been taking oestrogens before entry into the community, data on duration of usage must be considered incomplete. However, we did examine dose of conjugated oestrogens (dose being used for the longest period after entry into the community). When the living controls were used for comparison, high doses (1.25 mg or more) gave the same degree of protection as low daily doses (0.625 mg or less). When the deceased controls were used for comparison there was a suggestion of a dose-response effect, the risk ratio for women taking a high pill dose being 0.79 and that in women taking a lower pill dose being 0.39.

We used the linear logistic model to adjust for possible confounding by each of the variables listed in the table. There was little change in the risk ratio after allowing for any of these variables.

Only 30% of living controls had been frequent users of the medical clinic (>25 lifetime visits), compared with 52% of the cases and 52% of deceased controls. Adjusting for frequency of clinic use among the living controls decreased the observed risk ratio for conjugated oestrogen use, since more frequent clinic use was associated with an increased likelihood of recorded oestrogen use.

MATCHED RISK RATIOS FOR DEATH FROM ISCHAEMIC HEART DISEASE

	Living controls		Deceased controls	
Variable	No. of discordant pairs	Risk ratio	No. of discordant pairs	Risk ratio
Stroke	31	3·43**	32	2·20*
Hypertension	72	3·24***	80	2·33***
Angina pectoris	53	6·57***	42	2·50**
Myocardial infarction	50	7·33***	44	3·89***
Diabetes before age 65	11	2·67	14	2·50
Family history of heart attack	37	2·29	23	0·95
Cholesterol ≥300 mg/dl	25	1·27	24	3·00**
Cigarette smoking >1 pack/day	13	3·33*	20	1·00
Alcohol use	33	0·38**	45	0·88
Reserpine	52	2·06**	50	2·33**
Thiazide	66	2·30***	60	2·33**
"Other hypotensives"	78	4·57***	65	1·71*
Hypoglycaemics	21	6·00***	28	1·55
Cardiovascular preparations	79	12·17***	69	3·60***
Conjugated oestrogens†	57	0·43**	55	0·57*

*$p \leqslant 0.05$
**$p \leqslant 0.01$
***$p \leqslant 0.001$
†95% confidence intervals for use 0·24–0·75 (living) and 0·33–0·99 (deceased).

Discussion

Our results suggest that oestrogen replacement therapy in postmenopausal women may protect against death from IHD. The apparent protective effect was found by using two different types of, but closely age-matched, controls and was not explained by the presence of other risk factors for IHD. The effect was present in both necropsy-confirmed and non-necropsy-confirmed cases.

There are limitations to this study. We were unable to study the modification of risk by duration of use or the possible confounding or risk modifying effects of either age at menopause or type of menopause. However, in a previous case-control study in the community, oestrogen use did not correlate with age at menopause, and it was more likely in persons who had had an artificial menopause.[11] The frequency of artificial menopause is probably higher among the cases than among the controls,[2,3] and adjustment for this effect would be expected to further strengthen the observed protective effect.

Although we did not attempt to "blind" our medical record abstractor as to case or control status, it is unlikely that our findings resulted from abstraction bias, since we had no preconceived notion of what kind of change in risk of IHD would be brought about by oestrogen replacement therapy.

Most importantly, we were unable to study the possible confounding effects of changes in oestrogen usage following the development of IHD risk factors. Our concern that such a confounding effect might be present was based not only on

the possibility that different physicians may use different therapeutic criteria for oestrogen therapy but also on the possibility that differences in access to clinics and physicians may affect the likelihood of oestrogen usage. However, the risk ratio associated with oestrogen usage among those with no history of either previous myocardial infarction, stroke, angina pectoris, diabetes, or hypertension was similar to that among persons with a history of one or more of these risk factors. In addition, there was little evidence that frequency of oestrogen usage differed between cases with and without each of these risk factors when simultaneously controlled for frequency of clinic use. Moreover, when adjusting for the two measures of clinic use available to us, year of first use and frequency of use of the medical clinic, we found little effect on the observed risk ratios associated with oestrogen use. Cases and deceased controls had used the clinic with similar frequency and, not unexpectedly, living controls had used the clinic less.

Despite the limitations of the study, our findings, by the use of two independent control groups, of the presence of a negative association in all subgroups between oestrogen replacement therapy and IHD do suggest the possiblity of a cause-and-effect relationship, although the mechanism of this association is not obvious. Such a relationship would be consistent with trends in mortality rates. Menopausal oestrogen use has been widespread in the U.S. since the early 1960s.[10] Mortality rates from IHD began to decline in White females in the U.S. in the early 1960s, and by 1976 had decreased by over 30%, at a time when rates in White males decreased by almost 20%.[14] The decrease in rates among men was accompanied by a 26% decrease in proportion of cigarette smokers in the male population between 1964–75, but the reduction among females was only 8%. Over the same period, the percentage of women aged 55–64 with serum cholesterol greater than 260 mg/dl decreased by 29%, compared with 14% in men of the same age.[14]

Wallace et al., in a large cross-sectional study, found significant decreases in levels of serum low-density-lipoprotein cholesterol and very low density lipoprotein cholesterol and a significant increase in those of high-density -lipoprotein cholesterol in menopausal oestrogen users compared with non-users after adjustment for age, body mass, and education.[15] Others[16] have also noted a decrease in plasma cholesterol in menopausal oestrogen users. There also seems to be an association between oestrogen usage and hypercoagulability of the blood and an increased frequency of hypertension.[16,17] It is unclear whether oestrogen replacement therapy alters plasma lipid levels, or whether lipid levels are in some way associated with indications for oestrogen replacement therapy.

Age-adjusted death rates from IHD in White females in the U.S. are over four times the combined death rates of breast cancer and endometrial cancer. If the protective effect of oestrogen replacement therapy on risk of fatal IHD is real, this benefit would far outweigh the carcinogenic effects of oestrogens.

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NUTRITIONAL STATUS AND SEVERITY OF DIARRHOEA AMONG PRE-SCHOOL CHILDREN IN RURAL NIGERIA

ANDREW TOMKINS*

Endemic Diseases Research Unit, Malumfashi, Institute of Health, Ahmadu Bello University, Zaria, Nigeria; and Department of Human Nutrition, London School of Hygiene and Tropical Medicine, London

Summary   The influence of pre-existing malnutrition on the severity of diarrhoea was investigated by assessing attack-rate and duration of diarrhoea in children aged between 6 months and 32 months at the beginning of the rainy season in Malumfashi village area, northern Nigeria. There were 1·4 attacks of diarrhoea per child during the 3 month rainy season and children spent 10·5% of the time with diarrhoea. The frequency of diarrhoea was not increased in underweight (<75% weight/age) or stunted (<90% height/age) children, but those who were wasted (<80% weight/height) experienced 47% more episodes of diarrhoea than those who were not wasted. However, pre-existing malnutrition affected the duration of diarrhoea, which was 33% longer in underweight children, 37% longer in stunted children, and 79% longer in wasted children.

Introduction

DIARRHOEA is one of the commonest causes of mortality[1] and morbidity[2] among pre-school children in Malumfashi village area as in other parts of rural Africa.[3] A considerable proportion of children in this community become underweight during the second and third year of life.[4] A study in Bangladesh has demonstrated that malnutrition is associated with increased mortality from various infections including diarrhoea,[5] but the impact of malnutrition on morbidity is uncertain. In Guatemalan children the incidence of diarrhoea

*Present address: Medical Research Council Laboratories, Fajara, P.O. Box 273, Banjul, Gambia.

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