Intended for healthcare professionals

Papers

Impact of postmenopausal hormone therapy on cardiovascular events and cancer: pooled data from clinical trials

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Abstract

Objective: To examine the incidence of cardiovascular diseases and cancer from published clinical trials that studied other outcomes of postmenopausal hormone therapy as some surveys have suggested that it may decrease the incidence of cardiovascular diseases and increase the incidence of hormone dependent cancers.

Design: Trials that compared hormone therapy with placebo, no therapy, or vitamins and minerals in comparable groups of postmenopausal women and reported cardiovascular or cancer outcomes were searched from the literature.

Subjects: 22 trials with 4124 women were identified. In each group, the numbers of women with cardiovascular and cancer events were summed and divided by the numbers of women originally allocated to the groups.

Results: Data on cardiovascular events and cancer were usually given incidentally, either as a reason for dropping out of a study or in a list of adverse effects. The calculated odds ratios for women taking hormones versus those not taking hormones was 1.39 (95% confidence interval 0.48 to 3.95) for cardiovascular events without pulmonary embolus and deep vein thrombosis and 1.64 (0.65 to 4.18) with them. It is unlikely that such results would have occurred if the true odds ratio were 0.7 or less. For cancers, the numbers of reported events were too low for a useful conclusion.

Conclusions: The results of these pooled data do not support the notion that postmenopausal hormone therapy prevents cardiovascular events.

Key messages

The results of these pooled data do not support the notion that postmenopausal hormone therapy prevents cardiovascular events

These results concern only short term effects of postmenopausal hormone therapy, and long term effects may be different

There have been hundreds of trials studying the impact of hormones on various physiological phenomena, laboratory values, osteoporosis, symptoms, or various health problems but few fully report adverse effects. Small trials would be useful in studying unintended effects if they were more systematically reported

Introduction

Surveys suggest that postmenopausal hormone therapy (hormone replacement therapy) may decrease the incidence of cardiovascular diseases but increase the incidence of hormone dependent cancers—for example, breast cancer.[1 2 3 4 5 6] These findings are of major public health importance, and trials have been mounted to verify them, specifically to exclude the possibility of selection bias.[7 8] The results of these trials will not be available for some years, however, and current prescribing and use depend on individual interpretations of inadequate evidence and marketing factors. Surveys and observations of physicians show that many believe postmenopausal hormone therapy to be beneficial,[9 10 11 12] and in some countries the treatment has become very common.[13 14 15 16] Thus, further reliable information on health outcomes would be useful until the data from prospective trials are available.

We investigated the utility of information on cardiovascular events and cancer derived from published clinical trials studying other, short term, aspects of postmenopausal hormone therapy. This study was stimulated by the findings of the PEPI trial (the postmenopausal oestrogen/progestin interventions trial) on risk factors for heart disease.[17] Its table on adverse experiences showed a higher incidence of cardiovascular and thromboembolic events among users of the hormones (2.1 events/100 women) than in the placebo group (no events). This difference is not significant but is in the opposite direction of the pooled results of epidemiological surveys.

Methods

We searched for randomised trials that compared hormone therapy with placebo, no therapy, or vitamins and minerals in comparable groups of postmenopausal women. Hormone therapy was defined as oestrogens, in any form, alone or together with progestin/progesterone. Women given other types of active substances were not included in the comparison group. Trials were searched from Medline (1989 to November 1995) and reference lists of various review articles, books, and articles found. Languages accepted were English, German, the Scandinavian languages, and Finnish.

After identifying a trial with a comparable no hormone group we checked for any information on cardiovascular events (such as cardiac arrest, cerebrovascular accident, ischaemic attack, myocardial infarction), thromboembolic events (pulmonary emboli, deep vein thrombi), superficial phlebitis or thrombophlebitis, and cancers (breast, uterine body, other including cervical cancer and unspecified). We had also planned to study other health outcomes (such as gall bladder disease, mental symptoms, migraine, uterine diseases) but the definitions turned out to be either vague or varying, and they were not included. Trials with three months or more of treatment (specifically saying “no adverse events” or “no drop outs due to adverse events”) were included, and women from these trials contribute to the denominators. If the fate of all those who dropped out or the women lost to follow up was not clear, such a trial did not contribute to the denominator. Trials studying

the acute effects of oestrogens (three months or less of treatment) and crossover trials with treatment for three months or less in the first cycle were excluded. Trials with women who had undergone oophorectomy were specified separately. With the exception of the trial by Nachtigall et al,[18] cardiovascular and cancer outcomes were reported as incidental (reasons for drop outs or adverse effects). Such data were not given in summaries but required the reading of methods and results sections. Because of the large number of published studies on postmenopausal hormone therapy, we may have missed some pertinent trials, but this selection is unlikely to depend on the differential cardiovascular and cancer events by treatment groups.

We identified 22 pertinent trials (**Appendix 1**). Some trials—for example, the Danish trial from 1983-5—were included in several different reports, and their results were combined. Most trials concerned a very selective group of healthy women, but some included special subgroups. Because of the varying lengths of treatment, regimens used (see table 1), and the vagueness of describing health outcomes a formal meta-analysis was not carried out. Whether the data concerned numbers of patients or numbers of events was not always clear, but whenever possible, we took the numbers of patients. The number of women originally allocated to the groups was used as the denominator.

Reference	Regimens with daily doses	Women allocated	Cardiovascular disease*	Thromboembolic disease†
Speroff et al, 1996	Placebo	137	—	—
	Ethinyl oestradiol 1-10 µg	562	—	—
	Ethinyl oestradiol 1-10 µg+NETA 0.2-1 mg	566	—	—
Writing Group, 1995	Placebo	174	0	0
	CEE 0.625 mg	175	1	4
	CEE+MPA 10 mg/12 days	174	1	4
	CEE+MPA 2.5 mg	174	0	4
	CEE+ progesterone 200 mg/12 days	178	3	4
Aloia et al, 1995a,b	Placebo, calcium	≈78‡	—	—

Reference	Regimens with daily doses	Women allocated	Cardiovascular disease*	Thromboembolic disease†
	CEE 0.625+MPA 10 mg/10 days	≈39‡	—	—
Derman et al, 1995	Placebo	42	0§	—
	Oestradiol 2-1mg+NETA 1 mg/6 days	40	0	—
Tonstad et al, 1995	Placebo	32	—	—
	Oestradiol 2-1mg+NETA 1 mg/10 days	46	—	—
Wimalawansa, 1995	Calcium	14	1	—
	Transdermal oestradiol 1.5 mg+progesterone 200 mg/12 days	15	0	—
Munk-Jensen et al, 1988,1994; Obel et al, 1993	Placebo	51	—	—
	Oestradiol 2 mg+NETA 1 mg	50	—	—
	Oestradiol 2 mg/1 mg+NETA 1 mg/10 days	50	—	—
Lufkin et al, 1992	Placebo	39	—	—
	Transdermal oestradiol 0.1 mg+MPA 10 mg/10	36	—	—

Reference	Regimens with daily doses	Women allocated	Cardiovascular disease*	Thromboembolic disease†
	days			
Svendsen et al, 1992	Placebo	25	0	0
	Oestradiol 2 mg+cyproterone 1 mg	25	0	0
	Oestradiol 2 mg+levonorgestrel 75 µg	25	0	0
Gallagher et al, 1991	Placebo	19	—	—
	CEE 0.6 mg	20	—	—
	CEE 0.3 mg+MPA 10 mg	21	—	—
Genant et al, 1990¶	Placebo	40	—	—
	Oestrone sulphate 0.3, 0.625, 1.25 mg	116	—	—
Resch et al, 1990	Placebo	16	0	—
	Oestradiol 2 mg, NETA 1 mg	15	1	—
Molander et al, 1990	Placebo	19	—	0
	Oestriol 3 mg/2 mg	21	—	1
Christiansen et al, 1990	Placebo	20	1	—

Reference	Regimens with daily doses	Women allocated	Cardiovascular disease*	Thromboembolic disease†
	Oestradiol 2 mg+NETA 1 mg	20	1	—
Jensen et al, 1989* Hassager et al, 1987	Placebo	39	—	—
	Oestradiol 2 mg+cyproterone 1 mg/7 days	37	—	—
	Oestradiol 2 mg+NETA 1 mg	24	—	—
Riggs et al, 1982	Placebo, calcium	54	—	—
	CEE 0.625-2.5 mg	32	—	0
	CEE 0.625-2.5 mg+fluoride	28	—	0
Christensen et al, 1982**	Placebo	24	—	—
	Oestradiol 4 mg, oestriol 2 mg+NETA 1 mg/10 days	25	—	—
	Oestradiol 2 mg, oestriol 1 mg+NETA 1 mg/10 days	24	—	—
	Oestradiol 1 mg, oestriol 0.5 mg+NETA 1 mg/10 days	27	—	—
Christiansen et al, 1981**	Placebo (vitamin D3)	48	—	—

Reference	Regimens with daily doses	Women allocated	Cardiovascular disease*	Thromboembolic disease†
	Oestradiol 4 mg, oestriol 2 mg+NETA 1 mg/6 days	23	—	—
	Oestradiol 4 mg+vitamin D3	21	—	—
Coope, 1981	Placebo	26	0	—
	Oestrone sulphate	29	1	—
Christiansen et al, 1980**	Placebo	121	—	—
	Oestradiol 4 mg, oestriol 2 mg+NETA 1 mg/6 days	29	—	—
	Oestradiol+thiazide	27	—	—
Nachtigall et al, 1979	Placebo	84	3	1
	CEE 2.5 mg+MPA 10 mg/7 days	84	1	0
Lindsay et al, 1984	Placebo	30	0	—
	CEE 1.25, 0.625, 0.3, 0.15 mg	120	0	—
Aitken et al, 1973	Placebo	66	0	—
	Mestranol 40 µg	68	3	—

- CEE=conjugated equine oestrogen, NETA=norethisterone acetate, MPA=medroxyprogesterone acetate, 0=data explicitly mentioned but no cases found,—= data not mentioned. The trial of

Jensen et al, 1989 and the trials of Christensen et al, 1982, Christensen et al, 1981, and Christensen et al, 1980 possibly examine the same populations.

- *Includes cardiac arrest, ischaemic attack, myocardial infarction, heart failure, cerebrovascular accident.
- †Includes pulmonary embolus, deep vein thrombosis.
- ‡Exact numbers of women not given.
- §One pre-existing thromboembolic disorder was discovered.
- ¶Results not specified for oestrogen group.

Table 1
Details of numbers of women in trials of postmenopausal hormone therapy

Odds ratios (of the outcome in question with postmenopausal hormones divided by the outcome among controls) and their 95% confidence intervals were calculated by summing the events and denominators of the trials. Two different P values were calculated for cardiovascular diseases. The first one gives the probability of obtaining the calculated odds ratio when 0.7 (a hypothetical benefit concluded from previous literature) is assumed.[19] The second P value gives similar probability assuming the correct odds ratio to be 0.5.

Results

The types and dosages varied in different studies and, with the exception of the PEPI trial[17] and the trial by Speroff et al,[20] the numbers of women were small (table 1). In most reports the data on cardiovascular events and cancer were given incidentally, without description of how the event was defined, when it was detected, or how serious it was. Often all reasons for drop outs were not specified but said to be “unrelated to treatment.” Sometimes the timing of the event was given, especially if the event occurred very soon after the treatment. In most studies the data on cardiovascular events and cancers were available as reasons for dropping out and thus refer to numbers of patients. In the PEPI trial adverse events were given (110 events experienced by 97 women), and it is therefore possible that some women appear more than once in table 2.

Event	Hormone	Control	Odds ratio (95% CI)	P1	P2
Cardiovascular and thromboembolic:	17	6	1.64 (0.65 to 4.18)	0.04	0.01
Cardiovascular	12	5	1.39 (0.48 to 3.95)	0.10	0.03
Thromboembolic	5	1	2.89 (0.34 to 24.78)	0.10	0.05
Phlebitis	21	17	0.71 (0.37 to 1.35)	0.48	0.14

Event	Hormone	Control	Odds ratio (95% CI)	P1	P2
Breast cancer	19	9	0.85 (0.38 to 1.89)	NA	NA
Uterine cancer	2	2	0.58 (0.08 to 4.10)	NA	NA
Other cancers	12	8	0.86 (0.35 to 2.12)	NA	NA

- *Numbers of women in hormone and control groups trials 1818 and 1041.
- P1=probability of obtaining this odds ratio when 0.7 is true value.
- P2=probability of obtaining this odds ratio when 0.5 is true value.
- NA=not applicable.

Table 2
Numbers of women with events, with odds ratios and probability of finding observed odds ratio*

There were fewer women with cardiovascular and thromboembolic events in the groups who did not receive hormone therapy than in the groups who did (table **2**). The 95% confidence interval includes 1, but, as shown by the P values, it is unlikely that such a finding would have been found if the true odds ratio was 0.7. The likelihood of finding of an odds ratio of 1.64, if the true odds ratio was 0.7, is 0.04.

To see how sensitive the odds ratios were for inclusion of different kinds of trials we calculated odds ratios for each outcome in three other ways: excluding trials with oophorectomised women; excluding the trial by Nachtigall et al**18** (because the results of that trial differed from those of other trials notably); and also excluding the trials with less than one year of treatment. None of these calculations suggested that women receiving hormone therapy would have fewer cardiovascular events. In all analyses the difference in regard to thromboembolic events was larger than that for cardiovascular events.

Superficial thrombophlebitis was reported in only three trials. The incidence in the hormone group was higher in the PEPI trials and lower in the trial by Nachtigall et al**18**. Because reporting it as a reason for dropping out is less likely than for the more serious reasons it was not combined among the rest of thromboembolic diseases.

When we included all trials the rate of breast cancer was lower in the hormone group (table **2**). Only four women with uterine cancer (two in both groups) were reported (odds ratio 0.58). The number of uterine cancers in the hormone groups, however, is probably underestimated. It was commonly reported that women were excluded because of irregular or continuous bleeding or sometimes endometrial hyperplasia was reported. But the cause of the bleeding or outcome of hyperplasia was not specified.

Discussion

The results of these pooled (mostly) randomised data do not support the notion that postmenopausal hormone therapy prevents cardiovascular events. It is unlikely that the calculated odds ratios would have been found if

the true odds ratio was 0.7 or less. The numbers of women with events, however, as well as the total numbers of women were small.

There is no reason to believe that events were reported differently by group, but the absolute risk of adverse effects cannot be concluded. If the woman continued in the study an adverse effect would probably have remained unreported. Furthermore, in many trials women were lost to follow up, and even more trials gave no data on reasons or numbers of drop outs or losses to follow up. Most trials had selected only healthy women. Therefore the effects of postmenopausal therapy on sick women cannot be inferred from these results. This is especially noteworthy because currently many experts recommend hormone therapy for women either with cardiovascular diseases or those at high risk.

Our results concern short term effects of postmenopausal hormone therapy. It is quite possible that long term effects are different, both for cardiovascular diseases and for cancer. Short term effects on cardiovascular diseases are likely to occur through changes in blood viscosity, the arterial wall, and blood pressure and through cardiac arrhythmias. Long term effects—for example, because of blood lipids and various general physiological and psychological effects—may take years to have their impact. Breast cancer detected soon after a treatment—if it is related to the treatment—is likely to result from a promotion or activation of a pre-existing cancer. Carcinogenic effects or slower tumour promotion may take years or decades to show up.

The searches for this study revealed hundreds of trials studying the impact of hormones on various physiological phenomena, laboratory values, osteoporosis, symptoms, or health problems other than those of interest in this study. But usually they did not report adverse effects fully if at all. Pooled analyses, including meta-analysis, have greatly enhanced the usefulness of small trials in studying intended effects. The same could be true for adverse effects and other unintended effects, if they were always systematically reported.

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Conflict of interest: None.

Appendix

Papers revealed by searches

A table describing the following trials is available from EH.

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