

## SURVIVAL IN WOMEN RECEIVING HORMONE REPLACEMENT THERAPY. A RECORD-LINKAGE STUDY OF A LARGE POPULATION-BASED COHORT

PERSSON INGEMAR,<sup>1\*</sup> ADAMI HANS-OLOV,<sup>2</sup> BERGSTRÖM REINHOLD,<sup>3</sup>  
KRUSEMO ULLA BRITH<sup>4</sup> and HOOVER ROBERT<sup>5</sup>

<sup>1</sup>Departments of Gynecology and Obstetrics and <sup>2</sup>Surgery, University Hospital, Uppsala,  
<sup>3</sup>Department of Statistics, Uppsala University, Uppsala, <sup>4</sup>Uppsala University Data Center,  
Uppsala, Sweden and <sup>5</sup>National Cancer Institute, Rockville, Md, U.S.A.

(Received in revised form 9 November 1989)

**Abstract**—Survival was studied in a population-based cohort of over 23,000 women who were prescribed hormone replacement therapy. Complete follow-up through 1986 revealed a total of 1472 deaths, which was somewhat lower than expected; the relative survival being 101.1% (95% CL, 100.8, 101.3) after 5 years and 102.4% (95% CL, 101.9, 102.8) after 10 years. The relative survival increased with increasing age at entry into the cohort, being 98.2% (95% CL, 96.6, 99.8) in the 40–44 and 105.2% (95% CL, 101.4, 109.1) in the 65–69 year age group after 10 years. Neither the type of compound (potent vs non-potent estrogens), nor the year of entry into the cohort seemed to affect survival, whereas survival advantage generally increased with years of follow-up. Multivariate analysis showed that age at time of first prescription was the only determinant that significantly affected the death risk. This pattern could be explained by confounding due to selection of healthy subjects receiving hormone replacement therapy and/or by the specific choice of estrogen compounds (and progestogens), related to age. It is concluded that hormone replacement therapy is associated with a survival which is similar to or—notably at ages above 50–60 years—slightly higher than that in the general population.

Hormone replacement therapy    Survival    Cohort study

### INTRODUCTION

The use of non-contraceptive estrogens in women entails a variety of biological effects which could influence morbidity and mortality. The alleviation of vasomotor symptoms in the early postmenopausal period and of urogenital atrophic conditions in the late post-menopause by this treatment is well documented [1]. During recent years long-term estrogen treatment has

been reported to prevent postmenopausal bone loss and to reduce the risk of developing osteoporotic fractures by 50% [2]. Prophylactic measures are therefore recognized as a possible indication for estrogen use [3]. However, the increased risk of endometrial cancer [4] and a 1.5–2-fold increase in the risk of breast cancer after long-term exposure [5] needs serious consideration. Also, the effects on the risk of cardiovascular disease—the most important cause of death with advancing age [6]—are still controversial, since most [7–15], but not all [16–19] studies have shown that non-contraceptive estrogens have a protective effect, in

\*All correspondence should be addressed to: Ingemar Persson, M.D., Associate Professor, Department of Gynecology and Obstetrics, University Hospital, S-751 85 Uppsala, Sweden.

contrast to oral contraceptives, which have been found to be associated with an increased risk of cardiovascular events [20].

Against this background, studies with survival or all-cause mortality as an end-point seem particularly important for assessment of the overall impact of hormone replacement therapy. Reduced all-cause [21, 22] and cardiovascular mortality [15, 23] in women taking exogenous estrogens without progestogens has been reported. In the present study advantage was taken of the facilities available in Sweden for record-linkage studies, to conduct a large population-based cohort investigation, regarding survival, of women who had been prescribed both estrogens and estrogen-progestogen combinations.

#### MATERIALS AND METHODS

##### *The cohort*

In order to recruit a population-based cohort, prescription forms for estrogenic drugs were collected within the strictly defined Uppsala health care region in Sweden. This region comprises about 1/6 of the entire Swedish population of 8.4 million inhabitants. The pharmacies responsible for all drug sales in this region collaborated in a program designed so that all such forms for estrogenic drug prescription dispensed during a 3-year period from April 1977 through March 1980 would be sent to the study secretariat, as described in detail previously [24]. From each form thus received the following were computerized: the National Registration Number (a 10-digit number which exclusively identifies the individual and provides a means for record linkage); data for the prescribed estrogen (brand, dose, and package size); and the date of purchase.

Approximately 77,000 prescription forms were received, constituting approx. 92% of all such prescriptions dispensed at the pharmacies. The loss of registered forms was due to reporting failure at the pharmacies, estimated to be 4.6%, and exclusions on account of faulty National Registration Numbers on 4.6% of the reported forms [24]. This minor (random) loss of data from specific prescription forms does not necessarily lead to the exclusion of an individual woman, since in most cases more than one prescription form had been filled and on different occasions, and consequently not to selective loss with regard to any characteristic of the patient. The available material corresponded to 23,246 women, who met the follow-

Table 1. Numbers of cohort subjects in the different age groups and numbers of deaths among them during the follow-up period through 1986

Age at cohort entry (yr)	Number of women (%)	Number of deaths (%)
30-39	391 (1.7)	9 (2.3)
40-44	1369 (5.9)	45 (3.3)
45-49	4892 (21.0)	125 (2.6)
50-54	7475 (32.2)	251 (3.4)
55-59	4779 (20.6)	222 (4.6)
60-64	1879 (8.1)	138 (7.3)
65-69	1124 (4.8)	172 (15.3)
70-74	666 (2.9)	188 (28.2)
75+	643 (2.8)	322 (50.1)
	23,246	1472

ing eligibility criteria: one or more prescription forms for estrogenic drugs between April 1977 and March 1980; age 35 years or older at the time of purchase of the first recorded prescription; and residency in the Uppsala health care region. The age distribution of the women at entry into the cohort is shown in Table 1.

All cohort subjects were followed up for deaths through 1986 by linkage with the Causes of Death Registry, which provides the date of death for the whole of Sweden. In all, 1472 deaths were recorded in the cohort during the follow-up period in question (Table 1).

##### *Exposure characteristics of the cohort women*

Individual characterization among the entire cohort regarding exposure to estrogenic drugs was limited by the following factors: (1) the question of exposure before and after the prescription recording period, (2) the question of compliance with the drug prescription, and (3) the fact that no information about prescriptions for added progestogens was obtained for any of the cohort subjects. Nevertheless, the available prescription data provided a means of relating survival to approximate measures of exposure among all the cohort individuals.

A detailed description of exposure characteristics was achieved through a questionnaire study in a randomly selected sample (sub-cohort) of 735 cohort subjects in 1980 (89% response rate) [25] and in 1984 (84% response rate). By this means the exposure characteristics of the entire cohort could be estimated. 91% of the women who were prescribed estrogens reported actual intake of the drug; and a check of their registered prescription forms revealed that the majority of them (85%) had filled only one prescription, whereas among all those admitting ever use more than one prescription was recorded [24]; 50% of those receiving a

prescription in 1977 had started treatment before that year; oral intake was practised by 95% of the women; estradiol compounds (estradiol valerate 1–2 mg 51% and ethinylestradiol 10 µg 5%) accounted for 56% of all treatments, conjugated estrogens (0.625–1.25 mg) for 22% and other estrogens (mainly estriol compounds) for 22%; the choice of compounds was age-related, i.e. potent compounds (estradiol and conjugated estrogens) predominated before the age of 60 years and other estrogens at higher ages; the treatment indications varied with age, vasomotor problems being the main reason for treatment before the age of 60, and urogenital symptoms in older women; the proportion of women using combinations with progestogens varied with age, being about 45% at ages below 60 and 10% above; the median of treatment duration was 3.5 years at the end of 1983, at which time 21% of the women were current takers.

On the basis of prescription data only, three approaches were used to define exposure groups in this study, and each was motivated by findings based on the results from the sub-cohort questionnaire study:

(1) *Age at first recorded prescription, < 60 vs ≥ 60 years.* At ages below 60 years 84% of the women had, according to the sample questionnaires, used potent estrogens (estradiol compounds and conjugated estrogens) ever, chiefly for treatment of vasomotor symptoms, and in 34% estrogen-progestogen combinations, whereas at higher ages less potent compounds (mainly estriol compounds) only had been taken by 53%, for treatment of urogenital disorders.

(2) *Prescribed compounds—estradiol/conjugated estrogens ever vs other estrogens only.* Registration of prescriptions in the group which had ever received estradiol/conjugated estrogens was associated with 95% ever usage of these potent drugs and among 39% combined with progestogens, and in the group with other estrogens only, exposure to less biologically potent estrogens alone was present in 81% of the subjects.

(3) *Time of first recorded prescription, 1977 vs 1978–1980.* Prescriptions delivered in 1977 represented treatments that were ongoing in 50% of the women. The treatments tended to be of longer duration among those in the early period, i.e. 5.4 years vs 2.8 years in the late period, because of the impact of length biased sampling, and thereby were also of relatively long latency (time since treatment start). Those

recorded for the first time in 1978 and later probably represented newly started treatments, since a prescription form is valid for only 1 year.

#### *Characterization of risk factors*

Our assessment of the net effect of hormonal replacement therapy focused on relative survival rates, which adjust for the probability of dying from all causes in the general population. To be valid, this approach requires that the forces of mortality are equal in the study cohort and background population, except for the effects of the exposure. Any other factor associated with the risk of death that is unequally distributed between the two populations may therefore confound the relative survival estimates.

The sub-cohort questionnaire study [26] provided data on some factors that could be relevant to the risk of premature death (Table 2). A similar mailed questionnaire study was also conducted in an age-matched sample of 1239 women from the general population in the same geographical region [27]. A total of 952 subjects (77%) responded, of whom 850 had not been prescribed estrogens during the study period 1977–1980. Comparisons were made in two age groups, women of ages below and from 60 years (age in June 1978, corresponding to the mid-point of the cohort recruitment period).

It was found that in both age groups a higher proportion of women in the cohort than in the background population had undergone oophorectomy (and hysterectomy) (11.6 vs 2.9% and 7.3 vs 1.5%, respectively). A history of current smoking was more common in the younger age group (30.8 vs 22.7%). There was an indication that those below 60 years practised regular physical exercise more frequently, as did the comparison women. In both age groups the proportion of women, though low, with high school or university education was larger among the cohort women. With regard to body build (Quetelet's index), level of physical activity, prevalence of diabetes and hypertension, parity and mean age at menarche or menopause (data not shown), no differences relative to the background population were found.

#### *Statistical methods*

The observed survival rates for all causes of death were calculated by means of the actuarial or life-table method and the mortality in the cohort in relation to that in the general population was estimated by calculating the relative survival (RS) [28, 29]. RS is the ratio between

different  
age them  
1986

er of  
: (%)  
(2.3)  
(3.3)  
(2.6)  
(3.4)  
(4.6)  
(7.3)  
(15.3)  
(28.2)  
(50.1)

escription  
April 1977  
ler at the  
prescrip-  
health care  
women at  
ble 1.

d up for  
he Causes  
e date of  
all, 1472  
uring the  
l).

rt women  
the entire  
nic drugs  
s: (1) the  
r the pre-  
estion of  
1, and (3)  
criptions  
for any of  
available  
of relating  
exposure

character-  
questionnaire  
ple (sub-  
1980 (89%  
response  
acteristics  
ted. 91%  
estrogens  
d a check  
revealed  
filled only  
all those  
escription  
ceiving a

Table 2. Comparison of the distributions of specified factors (%) between the cohort (653 women) and the general background population (850 age-matched women)

Factor	Age <60 yr		Age ≥60 yr	
	Cohort	Population	Cohort	Population
<i>Bilateral oophorectomy</i>	11.6	2.9	7.3	1.5
<i>Hysterectomy</i>	19.4	7.1	16.9	7.1
<i>Smoking</i>				
Never	60.3	66.2	89.4	84.4
Previous	8.9	11.1	7.8	5.4
Current	30.8	22.7	7.8	10.2
<i>Quetelet's index*</i>				
<19	6.2	5.0	3.2	11.7
20-24	54.1	48.8	52.0	43.8
25-29	31.5	35.2	35.7	34.3
30-34	7.8	9.2	7.3	9.5
>35	0.4	1.8	1.6	0.7
<i>Daily physical activity</i>				
Sedentary	5.4	4.2	1.2	4.1
Low	25.2	23.6	15.9	13.4
Moderate	46.7	52.4	68.3	52.6
Heavy	22.7	19.8	14.6	29.9
<i>Physical exercise</i>				
None	33.1	33.6	47.7	34.7
Moderate	26.8	41.6	30.2	50.0
Regular	40.1	24.8	22.1	15.3
<i>Education</i>				
<8 yr	64.4	68.8	77.9	89.8
8-10 yr	23.4	24.7	13.9	12.4
High school	3.8	2.2	3.3	1.4
University	8.4	4.3	4.9	1.4

\*Weight (kg)/height (cm)<sup>2</sup>.

the observed survival in the cohort and the expected survival rate, which was obtained from the Swedish population tables by age (5-year intervals), sex and calendar year. The standard errors of the survival rates were calculated from Greenwood's formula [30], and 95% confidence limits were used to show the uncertainty of the estimates.

Relative survival estimates were firstly obtained in univariate and stratified analyses. Secondly, in order to separate the effect of one variable while adjusting for others, a multivariate Poisson regression model was applied [31].

If observed and expected death rates are all reasonably small, it can be shown that RS is approximately equal to

$$(1 + ED/PY) - D/PY,$$

where

ED = expected number of deaths

D = observed number of deaths

PY = person-years.

Thus, a multivariate analysis with excess death rate per 1000 person-years

$$[EXCD = 1000 (D/PY - ED/PY)]$$

as the dependent variable is consistent with use of the measure RS [32]. The excess death rate

was modelled as a linear function of age at first prescription, follow-up year, period of first prescription and type of compound. Age was given in categories of 35-44, 45-54, 55-64, 65-74 and 75+ years. The model was estimated on the assumption that the number of deaths has a Poisson distribution with use of the GLIM system [31]. The excess death rates were both positive and negative, which makes models that express the observed hazard as the sum of a general population (expected) hazard and a positive disease (treatment in this context) - specific hazard, unsuitable [33]. In addition to the Poisson regression models, weighted least squares regressions [32] were also performed for comparison. Results were similar.

## RESULTS

### *Univariate analyses*

In the whole cohort, progressively increasing cumulative RS rates were found during the period of follow-up. The rates (with 95% confidence limits) were 101.1% (100.8, 101.3) after 5 years and 102.4% (101.9, 102.8) after 10 years. The corresponding observed survival rates were 96.9% (96.6, 97.1) and 92.7% (92.3, 93.9) respectively (Table 3).

Table 3. Five- and ten-year cumulative observed (OS) and relative (RS) survival rates (and 95% confidence limits), overall, and by age at entry (date at 1st prescription), compound groups—estradiol and conjugated estrogens ever (E2/CE) and other estrogens only (OE)—and year of entry

Explanatory variables	5 yr		10 yr	
	OS (95% CL)	RS (95% CL)	OS (95% CL)	RS (95% CL)
<i>Overall</i>	96.9 (96.6, 97.1)	101.1 (100.8, 101.3)	92.7 (92.3, 93.1)	102.4 (101.9, 102.8)
<i>Age (yr)</i>				
35-39	98.5 (97.2, 99.7)	99.1 (97.8, 100.3)	97.6 (96.1, 99.2)	99.2 (97.6, 100.8)
40-44	98.2 (97.5, 98.9)	99.2 (98.4, 99.9)	95.7 (94.2, 97.3)	98.2 (96.6, 99.8)
45-49	98.8 (98.5, 99.1)	100.4 (100.0, 100.7)	97.0 (96.5, 97.6)	100.8 (100.2, 101.4)
50-54	98.4 (98.1, 98.7)	100.7 (100.4, 101.0)	96.2 (95.7, 96.7)	101.7 (101.2, 102.2)
55-59	98.1 (97.7, 98.5)	101.4 (100.9, 101.8)	94.5 (93.8, 95.3)	102.9 (102.0, 103.7)
60-64	96.8 (96.0, 97.6)	102.1 (101.2, 102.9)	91.8 (90.4, 93.2)	105.9 (104.2, 107.5)
65-69	93.3 (91.8, 94.8)	102.3 (100.6, 103.9)	81.3 (78.4, 84.3)	105.2 (101.4, 109.1)
70-74	85.7 (83.0, 88.4)	101.3 (98.1, 104.5)	63.9 (58.5, 69.3)	102.9 (94.2, 111.6)
75+	69.1 (65.4, 72.7)	106.0 (100.4, 111.6)	45.6 (40.9, 50.3)	136.4 (122.3, 150.4)
<i>Compound</i>				
E2/CE ever	97.9 (97.7, 98.2)	100.9 (100.7, 101.1)	94.8 (94.4, 95.2)	102.0 (101.5, 102.4)
OE only	93.7 (93.1, 94.4)	101.3 (100.7, 102.0)	86.5 (85.5, 87.6)	103.8 (102.5, 105.0)
<i>Year of entry</i>				
1977	97.2 (96.9, 97.5)	101.1 (100.8, 101.3)	93.3 (92.8, 93.8)	102.6 (102.0, 103.1)
1978+	96.4 (96.1, 96.8)	100.9 (100.5, 101.3)	92.6 (92.0, 93.2)	101.5 (100.9, 102.2)

Age at entry into the cohort was a determinant of RS (Fig. 1). In the age groups 35-39 and 40-44 years, RS was below 100% during the entire follow-up period, the values being 99.1% (97.8, 100.3) and 99.2% (98.4, 99.9) after 5 years and 99.2 (97.6, 100.8) and 98.2% (96.6, 99.8) after 10 years, respectively. In all

older age groups a survival advantage was noted, increasing with time and increasing age (Table 3, Fig. 1).

In the analysis of RS in groups formed with regard to types of compounds, estradiol/conjugated estrogens ever used vs other estrogens only, similar patterns were observed, but

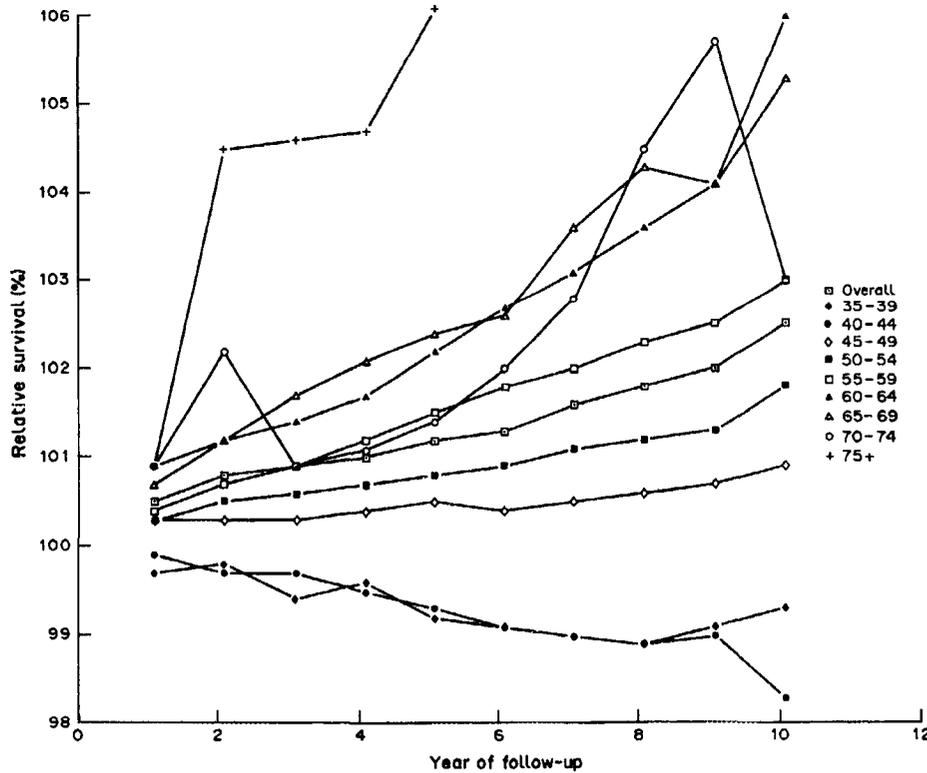


Fig. 1. Relative survival rates (RS), overall and in age groups (according to time at cohort entry), by duration of follow-up. All types of exposure.

age at first  
f first pre-  
was given  
65-74 and  
ed on the  
ths has a  
he GLIM  
were both  
odels that  
sum of a  
rd and a  
ontext) -  
ddition to  
hted least  
ormed for

increasing  
luring the  
95% con-  
.8, 101.3)  
2.8) after  
d survival  
.7% (92.3,

with a tendency to higher figures (though with no statistical significance) for the other estrogens than for the estradiol/conjugated estrogen group (Table 3, Fig. 2).

Women who had their first prescription registered during 1977 had slightly higher RS rates than those in 1978–1980 (Fig. 3, Table 3). For both groups, however, the RS rates were significantly higher than 100% (Table 3).

#### Stratified analysis

Among women prescribed estradiol compounds/conjugated estrogens, marked differences in RS rates were found with respect to age at first prescription. Again the age groups 35–39 and 40–44 had reduced RS—98.7% (96.8, 100.6) and 97.7% (96.0, 99.5), respectively, after 10 years—whereas all older age groups had RS rates higher than 100%, which increased with age and length of follow-up. Among those prescribed other estrogens only, no decrease in RS was found in any age, but there was a similar but less pronounced pattern with increments in RS with age (data not otherwise shown).

#### Multivariate analyses

Excess death rates were analysed in relation to the determinants included in the univariate analyses described above and also controlling for follow-up time. In Table 4 the results after a follow-up period of up to 10 years are given. In this multivariate model, age at first prescription was a strong determinant in itself of the risk of death. The excess death rate was significantly increased in the youngest age group relative to

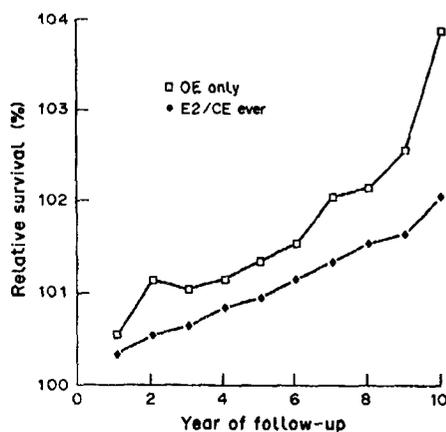


Fig. 2. Relative survival rates (RS) in groups according to type of prescribed compounds—estradiol/conjugated estrogens ever (E2/CE) and other estrogens only (OE), by follow-up time.

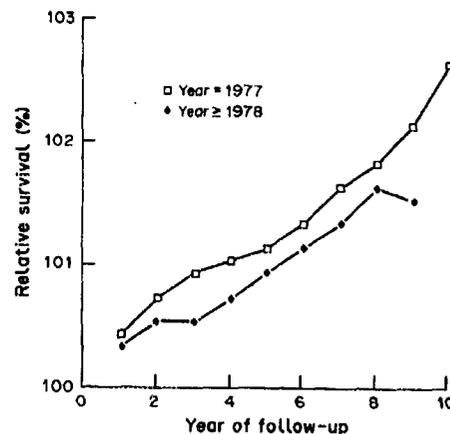


Fig. 3. Relative survival rates (RS) in groups according to year of entry (time of first prescription), 1977 and 1978–1980, by duration of follow-up.

the reference age group 45–54 years, but became progressively lower—thus with improvement in RS—with increasing age at cohort entry, with significant differences from 55 years onwards. Neither the type of compound—other estrogens vs estradiol/conjugated estrogens, nor the year of entry—late vs early—had a significant impact on the excess death rate.

In a separate model an analysis was made of those who had their first recorded prescription issued after 1978 (Table 5), and included follow-up time as a determinant of death risk. Again, age at time of first prescription—a surrogate variable for age at the true start of treatment in this subset of the cohort—showed a similar pattern, with incremental survival advantages with advancing age at start of treatment. The death risk did not seem to be influenced by the number of years of follow-up. The type of compound had no significant differential effect.

Table 4. Multivariate Poisson regression analyses of excess death rates, according to age at cohort entry (time of first prescription), type of compound—estradiol/conjugated estrogens ever (E2/CE) and other estrogens (OE) only—year of entry, and follow-up controlled for; follow-up 1–10 years

Explanatory variable	Excess death rate	95% CL
<i>Age (yr)</i>		
35–44	3.03	1.99, 4.07
45–54	0.00	reference
55–64	-1.90	-2.57, -1.23
65–74	-3.68	-6.17, -1.19
75±	-15.82	-24.21, -7.43
<i>Compound type</i>		
E2/CE ever	0.00	reference
OE only	0.46	-0.28, 1.21
<i>Year of entry</i>		
1977	0.00	reference
1978+	0.57	0.00, 1.14

Table 5. Multivariate Poisson regression analyses of excess death rates among women entering the cohort from 1978, according to age, type of compound—estradiol/conjugated estrogens ever (E2/CE) and other estrogens (OE) only—and follow-up period; follow-up 1–10 years

Explanatory variable	Excess death rate	95% CL
<i>Age (yr)</i>		
35–44	2.27	0.90, 3.64
45–54	0.00	reference
55–64	–2.39	–3.54, –1.24
65–74	–3.38	–6.99, 0.23
75+	–17.96	–29.07, –6.67
<i>Follow-up period (yr)</i>		
1–2	0.00	reference
3–4	0.07	–1.13, 1.27
5–6	0.17	–1.42, 1.08
7–8	–1.27	–2.54, 0.00
9–10	0.16	–2.94, 3.26
<i>Compound type</i>		
E2/CE ever	0.00	reference
OE only	0.24	–0.90, 1.38

#### DISCUSSION

The results of this study indicate that women prescribed hormonal replacement therapy overall have better survival than women in the population at large, with survival advantages of 1–2% after follow-up periods of 5–10 years. Analyses aimed at characterizing the determinants of the risk of death from all causes among these women showed that age at the time of the first estrogen prescription was the most powerful factor, in that increasing age entailed progressively improving survival. The age at first recorded estrogen prescription—which in the early part of the recruitment period (1977) represented ongoing treatment in half of the subjects and in the late part (1978–1980) commencement of treatment—can be regarded as a proxy variable for several exposure characteristics. Thus, women in the perimenopausal age groups and up to age 60 most frequently received potent estrogens such as estradiol and conjugated estrogens, often combined with cyclic progestogens, for vasomotor symptoms, and those at higher ages most frequently received the biologically weaker estriol compounds for urogenital atrophic conditions [25]. Multivariate analyses including all exposure variables revealed that age was the only significant determinant of the death risk among hormone users and that at ages below 55 this risk was unchanged or even somewhat increased. In themselves, the type of compound, period of first prescription and length of follow-up had no significant effect.

Thus, it seems that increasing age at which a women receives estrogens is associated with

increasing likelihood of survival compared with women in the general population of the same age. At large, these findings suggest that confounding by indication, i.e. selection with regard to forces of mortality other than the hormonal exposure, increased with advancing age at which treatment was started. Some data support this possibility. The comparison among women in the cohort samples and the background population showed differences in some factors that relate to health-oriented behaviour and the risk of death. Thus, among women aged 60 years and above, the prevalence of current smoking was lower and the level of education higher in the cohort than in the background population. Conversely, however, the higher prevalence of oophorectomies relative to the background population would rather increase the risk of death through an increased risk of death from cardiovascular causes [36]. In the below age 60 category survival seemed to be unaffected or slightly lower than expected. Selective health effects seemed less likely among these women, as there were less pronounced differences from the background population and the prevalence of current smoking was higher. Furthermore, a substantial proportion of these women were exposed to progestogens [25], which could have reduced the possible beneficial effects on lipoproteins and on the risk of cardiovascular mortality [34].

Survival could also have been affected by more intense medical surveillance among women seeking advice for menopausal symptoms as compared with other women. However, it is likely that all individuals would have easy and equal access to medical care under the Swedish medical system. Therefore, the influence of such a bias is judged to be minor.

The inability in a non-experimental study to measure the prevalence of all relevant risk factors for death among all individuals and to adjust for confounding effects in the analyses places limits on the interpretation of the results. However, the present design has important advantages. The cohort contributed a substantial sample size with a large number of deaths and the linkage with the National Causes of Death Registry ensured a complete follow-up. The cohort comprised virtually all women within one defined geographical region who had received hormone replacement therapy and comparison was based on national death rates, permitting unbiased estimates of relative survival.

according to  
1977 and  
p.

ut became  
vement in  
ntry, with  
nwards.  
estrogens  
r the year  
nt impact

s made of  
escription  
ed follow-  
ik. Again,  
surrogate  
atment in  
a similar  
dvantages  
nent. The  
enced by  
re type of  
tial effect.

ses of excess  
ry (time of  
l/conjugated  
only—year  
p 1–10 years

5% CL

99, 4.07  
reference  
57, –1.23  
17, –1.19  
21, –7.43

reference  
.28, 1.21

reference  
00, 1.14

ed by grants  
are grateful  
and Marsden

al. Estrogen  
11; 58: 267.  
al. Epidemic  
fractures.

phylaxis and  
1987; 295:

trial cancer.

Menopausal  
n expanded  
4: 825-832.  
ital Statistics  
ality, Part A.  
ublic Health  
984.

ill RD *et al.*  
pective study  
rdiovascular  
ol 1979; 54:

al. Effects of  
I. Metabolic  
525-536.  
he effects of  
omen. *Am J*

TM *et al.*  
tection from  
acet 1981; 1:

rdiovascular  
nent: a pilot  
1277-1278.  
al. Coronary  
omen. *Am J*

Estrogen use  
ontrol study.

al. Use of  
myocardial

GA *et al.*  
sal estrogen  
*Engl J Med*

MC *et al.*  
he Framing-  
17-161.  
ontraceptive  
tion. *JAMA*

Myocardial  
s in young  
tors. *JAMA*

WP. Post-  
oking, and  
er 50. *The*  
1985; 313:

ceptives and  
95-109.

21. 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: 903-906.
22. Hunt K, Vessey M, McPherson K *et al.* Long-term surveillance of mortality and cancer incidence in women receiving hormone replacement therapy. *Br J Obstet Gynecol* 1987; 94: 620-635.
23. Bush TL, Barrett-Connor E, Cowan LD *et al.* Cardiovascular mortality and non-contraceptive use of estrogen in women: results from the Lipid Research Clinics Program Follow-up Study. *Circulation* 1987; 75: 1102-1109.
24. Persson I, Adami HO, Johansson EDB *et al.* A cohort study of estrogen treatment and the risk of endometrial cancer. Evaluation of the method and its applicability. *Eur J Clin Pharmacol* 1983; 25: 625-632.
25. Persson I, Adami HO, Lindberg BS *et al.* Practice and patterns of oestrogen treatment in climacteric women in a Swedish population: a descriptive epidemiological study. Part I. *Acta Obstet Gynecol Scand* 1983; 62: 289-296.
26. Persson I, Adami HO, Lindberg BS *et al.* Characteristics of estrogen treated women. A descriptive epidemiological study of a Swedish population. Part II. *Acta Obstet Gynecol Scand* 1983; 62: 297-302.
27. Bergkvist L, Persson I, Adami HO *et al.* Risk factors for breast and endometrial cancer in a cohort of women treated with menopausal oestrogens. *Int J Epidemiol* 1988; 17: 732-737.
28. Ederer F, Axtell LM, Cutler SJ. The relative survival rate: a statistical methodology. *Natl Cancer Inst Monogr* 1961; 6: 101-121.
29. Haukalinen T, Abegwickroma KH. A computer program package for relative survival analysis. *Comput Prog Biomed* 1985; 19: 197-207.
30. Greenwood M. The errors of sampling of the survivorship table. In: *Reports on Public Health and Medical Subjects, Appendix 1, No. 33*. London: Her Majesty's Stationery Office; 1926.
31. Baker RJ, Nelder JAC. *The GLIM System; Release 3, Generalized Linear Interactive Modelling*, Oxford: Numerical Algorithms Group; 1978.
32. Pocock SJ, Gore SM, Kerr GR. Long term survival analysis. The curability of breast cancer. *Stat Med* 1982; 1: 93-104.
33. Hakulinen T, Teukanen C. Regression analysis of relative survival rates. *Appl Stat* 1987; 36: 309-317.
34. Hirvonen E, Malkonen M, Manninen V. Effects of different progestogens on lipoproteins during postmenopausal replacement therapy. *N Engl J Med* 1981; 304: 560-563.
35. Petitti DB, Perlman JA, Sidney S. Non-contraceptive estrogen and mortality: long-term follow-up of women in the Walnut Creek Study. *Obstet Gynecol* 1987; 70: 289-293.
36. Bush TL, Barrett-Connor E. Non-contraceptive estrogen use and cardiovascular disease. *Epidemiol Rev* 1985; 7: 80-104.