Pattern of mortality after menopausal hormone therapy: long-term follow-up in a population based cohort

Running title: menopausal hormone therapy and long-term mortality

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Abstract

Objective: To investigate long-term pattern of mortality in menopausal women according to different modalities of hormone therapy.

Design: Population based prospective cohort study.

Setting: Denmark 1993-2013.

Population: 29,243 women aged 50-64 years at entry into the Diet, Cancer, and Health Cohort, enrolled 1993-1997 and followed through December 31, 2013.

Methods: Cox' proportional hazards models for increasingly longer periods of follow up time were used to estimate mortality pattern according to baseline hormone use adjusted for relevant potential confounders.

Main Outcome(s): All cause and cause specific mortality. Outcome information was obtained from the Danish Causes of Death Registry (linkage 99.6%).

Results: 4,098 women died during a median follow-up of 17.6 years. After adjustment for relevant lifestyle risk factors, hormone use had no impact on all-cause mortality, regardless of modality. Among baseline users lower CVD mortality was only evident after 5 years (HR 0.54; 95% CI: 0.32-0.92), but dissipated with additional follow-up. Reversely, lower colorectal cancer mortality (HR 0.64; 95% CI 0.46-0.89), and higher breast cancer mortality (HR 1.34; 95% CI 1.05-1.72) only became evident after 15 years follow-up. There were no significant associations for mortality from other types of cancer or from stroke.

Conclusions: In this long-term follow-up study, taking hormones during menopause was not associated with overall mortality among middle-aged women. Investigating cause-specific mortality revealed significant albeit weak associations differential according to both causes of death and over time underlining the importance of carefully considering individual risks and duration of treatment when making decisions on hormone therapy.

Funding: This study received no funding.

Keywords: all-cause mortality, cause-specific mortality, menopausal hormone therapy, time-varying mortality estimates.

Tweetable abstract: long-term follow up study confirms no association between menopausal hormone therapy and overall mortality.

Introduction

Vasomotor symptoms such as hot flushes continue to affect a large proportion (>70%) of women going through menopause. [1] Hormone Therapy (HT) is the most effective treatment for vasomotor menopausal symptoms,[2] and prior to 2002 the proportion of women on HT was high. [3] However, after 2002 hormone use dropped dramatically [4, 5]. This was mainly in response to the initial reports from the large 'Women's Health Initiative' (WHI) randomised trials investigating HT as primary health prevention, which found that the health risks associated with HT outweighed the benefits[6]. Despite finding an overall increased health risk among the women in the intervention arms, neither regimen has shown any effect on all-cause mortality neither in initial reports[7] nor subsequently with increasingly longer follow up (13.2 years) [8] and (18 years)[9].

In the most recently published Cochrane systematic review investigating the effect of HT>1 years only a slight increase in lung cancer specific mortality was noted (1-8 extra cases per 1000 women on HT) but no effect on overall or other cause-specific measures of mortality was found[10]. However, the authors also note that the current evidence base is heavily dominated by the large WHI primary and HERS secondary prevention trials [11, 12].

Even though these trials represent the highest quality evidence, the nature of their design (testing only single regimens and mainly for prevention), the fact that they were stopped early, and the demographic profile of participants (older age and existing disease), hinders a proper assessment of the impact of hormones used around menopause on long-term mortality[10]. Further, considering how several risk associations seem to dissipate while others appear with longer follow-up it is relevant to analyse the distribution of events and potentially time-varying magnitude of associations during follow up in more detail[13].

Using a large population-based prospective cohort with data on hormone use collected prior to 2002, this study investigates the associations between hormone used around menopause and all cause and cause specific mortality during 20 years of follow up.

Methods

Population

The Diet, Cancer, and Health Cohort is a large Danish population based study established between 1993 and 1997. Of the 79,729 women (aged 50-64 years and without a previous cancer diagnosis) invited 29,875 (37%) participated (corresponding to 7% of the Danish female population in the given age group). A more detailed description of the cohort has been published previously.[14] Each participant was followed from baseline (the date of first study clinic visit) until either date of death, date of emigration, or December 31, 2013, whichever came first. Figure S1 (online supplement) gives an overview of study in-, and exclusions as well as the final sample distribution into different outcomes.

Measurements

Participants completed two self-administered questionnaires at baseline. Descriptions of the development and validation of the questionnaires have been published previously. [15, 16] Anthropometric measurements were obtained by professional staff members at a study clinic visit, where various biological specimens were also sampled from participants.

Exposure

In the questionnaires the women gave information about HT (never/previous/current use) and, if relevant, the age at which they started HT. From women who indicated either previous or current hormone use information on duration as well as route of administration (tablets/injections/skin depot/skin patch/vaginal) was used for further analysis. Women with ≤6 months of use were categorized as “triers”. The route of administration was categorized as ‘oral’ (incl. any combination with others); ‘other systemic’ (all non-oral HT); ‘only local’ (only vaginal treatment). Current users also provided the brand name of the

101 therapy they currently used. Based on these self-reported brand names the type of HT was divided into
102 'oestrogen alone', 'combination therapy' (oestrogen and progestogen) (further subdivided into sequential
103 or continuous regimens), or 'unspecified' if no brand name was given. Investigations from a sub-sample of
104 participants including serum sex hormone measurements previously conducted in the cohort showed good
105 correlation between self-reported HT and serum sex hormone blood levels.[17]

106 **Outcome**

107 Cohort members were linked via their unique national personal identification numbers to the Danish
108 Causes of death registry. [18] ICD-10 diagnoses for different causes of death were categorized into 'cancer'
109 (ICD C diagnoses, and subdivided into separate types of cancer), 'CVD' (all I diagnoses), 'unknown' (R960-
110 R999), and 'others' (all remaining recorded ICD-10 codes). Completeness of follow up on mortality was
111 99.6% (131/29,875 emigrated).

112 **Covariates**

113 The following covariates were considered as possible confounders for inclusion into the regression analyses
114 based on à priori hypotheses of associations with the outcome.
115 Alcohol intake; categorized into average lifetime daily intake since age 20 using baseline age and a
116 cumulative measure 'alcohol drinking years' (1 dy=an average of 1 unit (10g alcohol)/day/year since age
117 20), and divided into 6 categories. ("lifetime abstainers"; minimal intake (0 dy); <0.5 unit/day; 0.5-1 unit per
118 day; 1-2 units/day, and >2 units/day). Smoking; recorded as "never", "previous" or "current" smokers at
119 baseline. Physical activity; recorded as leisure time activity and divided into a binary variable of "active" vs.
120 "inactive". BMI was divided into 4 categories according to WHO definitions (< 18.5 "underweight"; 18.5-
121 24.99 "normal weight"; 25-29.99 "overweight", ≥30 "obesity (class 1-3)",[19] education level based on
122 duration of schooling was used as an indirect measure for socioeconomic position; divided into short (≤7
123 years), medium (8-10 years), or long (≥10 years) duration of education. Table S1A shows crude and
124 different adjustment level models.

125 **Statistical Methods**

The associations between HT and mortality were assessed using Cox' proportional hazards models with age as the underlying time scale, while adjusting for time of recruitment as well. We created three different models; one for each exposure parameter ('over all use'; 'type of HT used'; and 'route of administration'). 'Never users' was the reference group in all analyses. To capture the distribution of events and potentially time-varying magnitude of associations during follow up[13] we also calculated HRs for increasingly longer periods of follow up time (5-, 10-, 15-, and 20 years of follow up). Competing risk regression models according to the method of Fine and Gray[20] were also done to compare estimates in the models of cause specific mortality, where different causes of death, at least in theory, can act as competing risks[21]. All tests were based on log likelihood ratio test statistic and confidence intervals calculated with Wald's test. All analyses performed with STATA version 14.

Ethics

The ''Diet, Cancer and Health'' study has been approved by the relevant Scientific Committees and the Danish Data Protection Agency. Informed consent was obtained from all participants to search information from medical registers including the Danish Causes of death registry[14].

Participant & Public Involvement

No participants were involved in setting the research question or the outcome measures, nor were they involved in developing plans for recruitment, design, or implementation of the study. No participants gave advice on interpretation or writing up of results.

Funding

The study received no funding.

Results

The characteristics of the study population and baseline hormone use are summarized in Table 1. At baseline, 54.4% (15,904/29,243) of the women had never used hormones, 15.5 % (4,532/29,243) were previous users, and 30.0% (8,771/29,243) of the women currently used hormones. Among women using hormones at baseline 2,671 used estrogen alone, 1,867 combined continuous, and 3,212 combined sequential hormone preparations. Most of the women using hormones (previously or at baseline) took orally administered hormones (n= 11,559). 1,147 women took a combination of oral and local, and only 597 took only local hormones.

A total of 4,098 participants died during a median follow-up of 17.6 years (SD 2.9 years), and of these 2,155 died from cancer (222 died from colorectal cancer, 308 from breast cancer, 576 from lung cancer, 163 from ovarian cancer, 36 from endometrial cancer, and another 850 from other cancers). 671 women died from CVD (203 died from ischemic heart disease, 209 from stroke, and 259 from other CVD related causes). The remaining 1,084 women died from other causes. For 188 participants the cause of death was unknown (see Figure S1 (online supplement), and table 2).

After adjustment for relevant lifestyle risk factors, hormone use had no impact on all-cause mortality, regardless of type or route, at end of follow up (see Table 2).

When looking more closely at specific causes of deaths, at the end of follow up, no differences in cancer specific mortality or mortality from other causes were seen between women on HT and never users(Table 2). When further subdividing into death due to specific causes of cancer and specific causes of cardiovascular diseases colorectal cancer mortality was markedly lower among both current and previous users (HR 0.64, 95% CI 0.46 to 0.89, and HR 0.67, 95% CI 0.46 to 0.99, respectively), when compared to never users (Table 3). This lower mortality was also seen across the remaining measures of hormone use, and statistically significant ‘oral hormone use’ and ‘oestrogen only’. The opposite was seen for breast cancer mortality, where current users had significantly higher mortality as compared to never users (HR

1.34, 95% CI 1.05 to 1.72). This was also for oral use (HR 1.29, 95% CI 1.03 to 1.63). The combined continuous type of HT was also significantly associated with higher BC mortality (HR 1.56, 95% CI 1.05 to 2.31), whereas the association between oestrogen only and breast cancer mortality, although in the same direction, was not statistically significant (HR 1.37, 95% CI 0.95 to 1.98).

The category of 'only local' HT use was associated with higher risk of IHD as cause of death, however there were few women in this subgroup and hence the associations difficult to interpret. No associations were seen for other types of cancer specific mortality or death from stroke.

Conducting Fine and Gray competing risk regression yielded parameter estimates similar to the ones obtained in the Cox' regression model (see table S1B).

During follow up, several time-varying effects of HT on cause specific mortality were evident (Figure 1). There was an initially, significantly lower CVD mortality among current users compared to never users (HR 0.54, 95% CI 0.32 to 0.92). This, however, dissipated with longer follow up (HR at 10 years: 0.78, 95% CI 0.58 to 1.06, and HR at 15 years: 0.92, 95% CI 0.74 to 1.14). Conversely, the lower CRC and higher BC mortality estimates only became evident after 10 years of follow up (CRC: HR at 10 years 0.67, 95% CI 0.41 to 1.09; BC HR at 10 years 1.24, 95% CI 0.82 to 1.87), statistically significantly so after 15 years of follow up (CRC HR at 15 years 0.65, 95% CI 0.46 to 0.93; BC HR at 15 years 1.33, 95% CI 1.00 to 1.77) (see Figure 1).

Discussion

Main findings

In this observational study of 29,243 Danish women, with a median age of 56 at entry and followed up for over 17 years on average, a significantly higher risk of breast cancer mortality but lower risk of colorectal cancer mortality was seen among women using HT compared to never users. There were no evident associations between HT and other causes of death. In summary, this resulted in no association for all-cause mortality. The development in mortality estimates during follow up diverged over time with the lower colorectal and higher breast cancer mortality only becoming evident after 15 years, while the initially lower CVD mortality dissipated.

Strength & Limitations

This was a large, population-based cohort with long and almost complete (99.6%) follow up on mortality outcomes and with detailed and validated information on exposures and potential confounders. Further, data on hormone use was collected prior to the dramatic drop seen after WHI results became official in 2002, and since most of the participants were well past menopause in 2002 (median age at end of 2002 was 63.1 years (5-95% range 57.2 to 71.1)) they should be largely unaffected by this.

The major limitations include the observational nature of the data and hence the possible influence of residual confounding. 'Healthy users' selection is also of concern. To minimise this, we divided hormone use into current and previous use. Further, we saw no difference in the associations for current users, who recently initiated HT, and those with a longer interval between HT initiation and baseline (data not shown). Nevertheless, selection is unavoidably introduced when excluding women with morbidities relevant for the outcomes, and when susceptible women dying before potential recruitment could not be included. This most likely bias the associations towards the null-hypothesis. Information on brand names were not given by 11.6% (1,021/8,771) of the current hormone users. In addition, most women in the cohort took HT as oral medication, which hindered meaningful comparisons of different routes of administration. Finally, a

major limitation is the single point measurement of hormone use rendering changes in use after baseline unknown. This might introduce some exposure misclassification, especially if women switched between treatments. Some misclassification of cause of death also cannot be excluded, however, such misclassification is believed to be minimal[22] and would only influence the cause specific estimates and not the overall mortality measure.

Interpretation

Despite the complex risk profile of HT reported from both major randomised trials and observational studies, when considering the aggregate effect of hormone use without consideration to specific subgroups of treatment or participants, the overall null effect on mortality found in this study concurs with most previous studies[9, 23, 24]. In contrast, a meta-analysis of studies of only younger women (<60 years) incl. those in the young age strata in the WHI trial (50 to 59 years) found an overall reduced mortality among women taking HT[25], primarily attributed to reductions in CVD mortality[26]. In the present cohort, which by these definitions, consists mostly of younger women (median age at entry 56.2 years), a lower CVD mortality was only seen initially (after 5 years of follow-up), however no difference in overall mortality was observed. Part of the reason for this difference might be due to a different disease distribution; in this cohort, breast cancer comprised 36.3% (1,996/5,503) of all cancers, which is relatively higher than the estimated European average of 28.8% [27], and the higher mortality from breast cancer would counter the lower mortality seen from other causes. The substantially longer follow up in this study allowed for better estimation of mortality from postmenopausal breast cancer, which is generally more slowly progressing than other cancers. In addition, a particularly prolonged recurrence pattern is seen among receptor positive breast cancer[28], which is also more common in women with previous HT use[29-31]. In this cohort, the median time (independent of exposure status) between BC diagnosis and death was 1,673 days (5-95%: 175 to 4,969 days). Indeed, when looking more closely at the development in mortality estimates during follow up a pattern of initially lower CVD mortality, which then dissipated during additional follow up was evident,

whereas the difference in cancer mortalities found to be associated with HT only became clear after much longer follow up.

The WHI combination trial also found a borderline significant increase in breast cancer mortality (HR 1.44 95% CI: 0.97 to 2.15)[9]. However, paradoxically, a lower breast cancer specific mortality was seen among women in the estrogen alone trial HR 0.55 (0.22-0.92) (based on 63 deaths)[9]. A potential explanation for this finding has been suggested to be different effects on breast cancer detection, which seems to be hindered among women on combined therapy but not among those on estrogen alone[32] but the exact mechanisms behind this observation remain undetermined[33].

HT use has been associated with a lower colorectal cancer (CRC) incidence in both intervention and observational studies. A recent meta-analysis found an overall significantly lower risk of CRC for both types of hormone use (summary HR 0.83; 95 %CI: 0.79 to 0.88) and no differences depending on type or duration[34]. In the WHI since the reduced CRC incidence did not translate into reduced CRC mortality[35], it was interpreted as diagnostic delay rather than a clinically meaningful benefit of HT for preventing CRC[36]. Observational studies evaluating HT as chemoprevention published after the WHI all reported lower CRC risk similar to ours[37]. Worth noting is that most of these studies found the strongest association after longer duration of use, whereas short term use did not seem to have long lasting effects, just as was suggested in the WHI[7], and hence possibly the reason for this discrepancy. However, it cannot be excluded that a differential selection of less susceptible women over time, at least in part, explain why the HRs diminish with prolonged follow up rather than a truly preventive effect of HT being the cause[13].

The weak associations reported between HT and lung cancer mortality was based primarily on the results from WHI[10], which found an increased risk of lung cancer death in women on combined therapy after 8 years of cumulative follow up (based on 73 deaths (intervention) vs. 40 deaths (placebo))[38] but attenuated with additional follow up[39]. No such association was found in this study despite a substantially larger number of lung cancer related deaths (n=576) and much longer follow up. Due to limited number of ovarian cancer deaths, the power to study the association between hormone use and ovarian cancer

mortality was insufficient, which was also the case for other less common causes of death such as those related to neurological and psychiatric disorders, which has been suggested in early studies[40].

Conclusion

As several previous studies have indicated, this long-term follow up study confirmed that taking hormones during menopause was not significantly associated with overall mortality among middle-aged women. Investigating cause-specific mortality and development in estimates during follow up revealed differential associations in both causes of death and time specific associations with a slightly higher breast cancer mortality opposed by lower colorectal cancer mortality in the long term, and lower CVD mortality mainly in the short term. This divergent mortality pattern underlines the importance of carefully considering individual risks when making decisions on hormone therapy.

Contribution to authorship: MH and AO conceived the study idea. MH designed and performed all the data analyses with advice from SAY, AO and AT. MH drafted the manuscript. MH, AO, SAY, KO, ØL, NK and AT contributed to additional writing, discussing and commenting on the paper.

Disclosure of interests: Lidegaard has received honoraria for speeches in pharmaco-epidemiological issues within the last three years. For all remaining authors no conflicts of interest declared. Completed disclosure of interest forms are available to view online as supporting information.

Details of ethical approval: The ‘‘Diet, Cancer and Health’’ study has been approved by the relevant Scientific Ethical Committees and the Danish Data Protection Agency (J-nr. 2013-41-2043; Nov. 24, 2014). Informed consent was obtained from all participants to search information from medical registers including the Danish Causes of death registry.

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Supporting information: Additional supporting information may be found in the online version of this article: Figure S1, Table S1A and S1B.

Table 1. Participant demographics and lifestyle according to hormone therapy in the Diet, Cancer, and Health Cohort study.

Hormone therapy		All	%	never	%	previous	%	current	%
N		29,243	-	15,904	54.4	4,532	15.5	8,771	30.0
Deceased,		4,098	14.0	2,132	13.4	735	16.2	1,231	14.0
Age, median, (5-95%)		56 (50-64)		55 (50-64)		57 (51-64)		56 (50-64)	
Education level									
	Short (≤7 years)	9,155	31.3	4,991	31.3	1,631	36.0	2,533	28.9
	Medium (8-10 years)	14,678	50.2	7,97	50.0	2,202	48.6	4,506	51.4
	Long (≥10 years)	5,41	18.5	2,979	18.7	699	15.4	1,732	19.7
BMI									
median, (5-95%)		24.8 (19.9-33.8)		24.9 (19.9-34.5)		25.4 (20.1-34.3)		24.3 (19.8-32.0)	
	Underweight (<18.5)	369	1.3	198	1.2	49	1.1	122	1.4
	Normal (18.5-24.99)	14,489	49.5	7,729	48.5	1,956	43.1	4,804	54.8
	Overweight (25-29.99)	10,198	34.9	5,437	34.1	1,790	39.5	2,971	33.9
	Obese (≥30)	4,187	14.3	2,576	16.2	737	16.3	874	9.9
Smoking									
	Never	12,776	43.7	7,444	46.7	1,746	38.5	3,586	40.9
	Previous	6,866	23.5	3,563	22.4	1,110	24.5	2,193	25.0
	Current	9,601	32.8	4,933	30.9	1,676	37.0	2,992	34.1
Alcohol intake									
Drinking years[a] among drinkers median, (5-95%)		21.8 (4.5-75.7)		20.8 (4.2-73.1)		22.6 (4.7-74.2)		23.4 (4.8-79.6)	
Average lifetime intake[b]									
	<0.5 U/day	12,601	43.1	6,998	43.9	1,959	43.2	1,162	43.5
	0.5-1 U/day	6,883	23.6	3,763	23.6	1,026	22.6	604	22.6
	>1-2 U/day	5,042	17.2	2,617	16.4	777	17.2	448	16.8
	>2 U/day	1,943	6.6	980	6.2	274	6.1	187	7.0
	Minimal intake (less than one drinking years[1])	2,506	8.6	1,417	8.9	455	10.0	245	9.2
	Lifetime abstainer	268	0.9	165	1.0	41	0.9	25	0.9
Physical activity									
	Active	17,067	58.4	9,201	57.7	2,586	57.1	5,280	60.2
	Unknown	280	1.0	157	1.0	34	0.8	89	1.0
median, (5-95%) in active		1.5 (0.5-6)		1.5 (0.5-6)		1.5 (0.5-5.5)		1.5 (0.5-6)	

[a]drinking years (1 unit (10g ethanol)/day in 1 year), [b]average daily intake between age 20 and baseline: based on drinking years and age.

Table 2. Hazard ratios and 95% confidence intervals for the associations between hormone therapy and overall and cause specific mortality.

Hormone therapy	Level	n events[a]	Overall mortality HR[b] (95% CI)	n events[a]	Cancer mortality HR[b], (95% CI)	n events[a]	CVD mortality HR[b], (95% CI)	n events[a]	Other mortality HR[b], (95% CI)
n, events[a]		4,098		2,155		671		1272	
Overall use									
	Never	2,132	1.00	1,126	1.00	356	1.00	650	1.00
	Current	1,231	1.00 (0.93-1.07)	657	1.00 (0.91-1.11)	187	0.93 (0.78-1.11)	387	1.03 (0.91-1.17)
	Previous	735	1.00 (0.92-1.09)	372	1.00 (0.88-1.11)	128	0.99 (0.81-1.21)	235	1.03 (0.88-1.19)
Route									
	No HT	2,132	1.00	1,126	1.00	356	1.00	650	1.00
	Oral	1,738	1.01 (0.95-1.08)	916	1.02 (0.93-1.11)	273	0.95 (0.81-1.11)	549	1.04 (0.93-1.16)
	Other systemic	160	0.95 (0.81-1.11)	80	0.92 (0.73-1.15)	25	0.85 (0.57-1.28)	55	1.05 (0.80-1.38)
	Only local	68	0.90 (0.71-1.15)	33	0.81 (0.57-1.15)	17	1.38 (0.84-2.24)	18	0.81 (0.51-1.29)
Type									
	No HT	2,132	1.00	1,126	1.00	356	1.00	650	1.00
	Estrogen only	393	0.99 (0.89-1.11)	212	1.02 (0.88-1.19)	69	1.04 (0.80-1.35)	112	0.92 (0.75-1.12)
	Combined, continuous	292	1.02 (0.90-1.15)	166	1.11 (0.94-1.30)	38	0.81 (0.58-1.14)	88	0.98 (0.78-1.23)
	Combined, sequential	415	1.01 (0.91-1.12)	224	1.00 (0.87-1.16)	56	0.86 (0.64-1.14)	135	1.11 (0.92-1.34)
	Unspecified incl. previous users	866	0.99 (0.92-1.08)	427	0.96 (0.85-1.06)	152	1.00 (0.83-1.21)	287	1.06 (0.92-1.22)

[a] events=deaths; [b]adjusted for age, alcohol, smoking, bmi, physical activity, and level of education

Table 3. Hazard ratios and 95% confidence intervals for the associations between hormone therapy and selected cause specific mortality.

Hormone Therapy	Level	n events[a]	Colorectal cancer HR[b], (95% CI)	n events[a]	Breast cancer HR[b], (95% CI)	n events[a]	Ischemic HD[3] HR[b], (95% CI)	n events[a]	Stroke HR[b], (95% CI)
n, events[a]			222		308		203		209
Overall use									
	Never	140	1.00	146	1.00	105	1.00	106	1.00
	Current	51	**0.64 (0.46-0.89)**	113	**1.34 (1.05-1.72)**	55	0.96 (0.69-1.33)	68	1.11 (0.82-1.51)
	Previous	31	**0.67 (0.46-0.99)**	49	1.05 (0.76-1.46)	43	1.09 (0.77-1.56)	35	0.94 (0.64-1.38)
Route									
	No HT	140	1.00	146	1.00	105	1.00	106	1.00
	Oral	72	**0.66 (0.49-0.88)**	148	**1.29 (1.03-1.63)**	84	1.00 (0.75-1.33)	92	1.07 (0.81-1.42)
	Other systemic	7	0.66 (0.31-1.40)	8	0.74 (0.36-1.50)	5	0.55 (0.22-1.34)	8	0.95 (0.46-1.95)
	Only local	3	0.54 (0.17-1.71)	6	1.06 (0.47-2.40)	9	**2.74 (1.38-5.44)**	3	0.75 (0.24-2.36)
Type									
	No HT	140	1.00	146	1.00	105	1.00	106	1.00
	Estrogen only	14	**0.55 (0.32-0.96)**	36	1.37 (0.95-1.98)	23	1.20 (0.76-1.88)	26	1.29 (0.84-1.99)
	Combined, continuous	11	0.60 (0.32-1.11)	30	**1.56 (1.05-2.31)**	9	0.69 (0.35-1.37)	16	1.10 (0.65-1.87)
	Combined, sequential	22	0.82 (0.52-1.28)	37	1.27 (0.88-1.83)	13	0.70 (0.39-1.24)	18	0.90 (0.54-1.45)
	Combined, all	33	0.73 (0.50-1.07)	67	**1.38 (1.03-1.85)**	22	0.69 (0.44-1.10)	34	0.98 (0.67-1.45)
	Unspecified incl. previous users	35	**0.64 (0.44-0.92)**	59	1.05 (0.78-1.42)	53	1.16 (0.83-1.61)	43	0.98 (0.69-1.40)

[a]events=deaths; [b]adjusted for age, alcohol, smoking, bmi, physical activity, and level of education, [3]Heart disease.

No associations found with other cancers including lung (576 failures), ovarian (163 failures), or endometrial (36 failures).

	5 years of follow up			10 years of follow up			15 years of follow up			20 years of follow up		
	n	HR[a]	95% CI	n	HR[a]	95% CI	n	HR[a]	95% CI	n	HR[a]	95% CI
Mortality	510	0.85	0.69, 1.05	1479	0.94	0.84, 1.06	2931	1.00	0.92, 1.08	4,098	1.00	0.93, 1.07
CVD mortality	**94**	**0.54**	**0.32, 0.92**	253	0.78	0.58, 1.06	469	0.92	0.74, 1.14	671	0.93	0.78, 1.11
CRC mortality	36	1.05	0.51, 2.17	98	0.67	0.41, 1.09	**179**	**0.65**	**0.46, 0.93**	**222**	**0.64**	**0.46, 0.89**
BC mortality	33	0.67	0.28, 1.60	114	1.24	0.82, 1.87	**230**	**1.33**	**1.00, 1.77**	**308**	**1.34**	**1.05, 1.72**

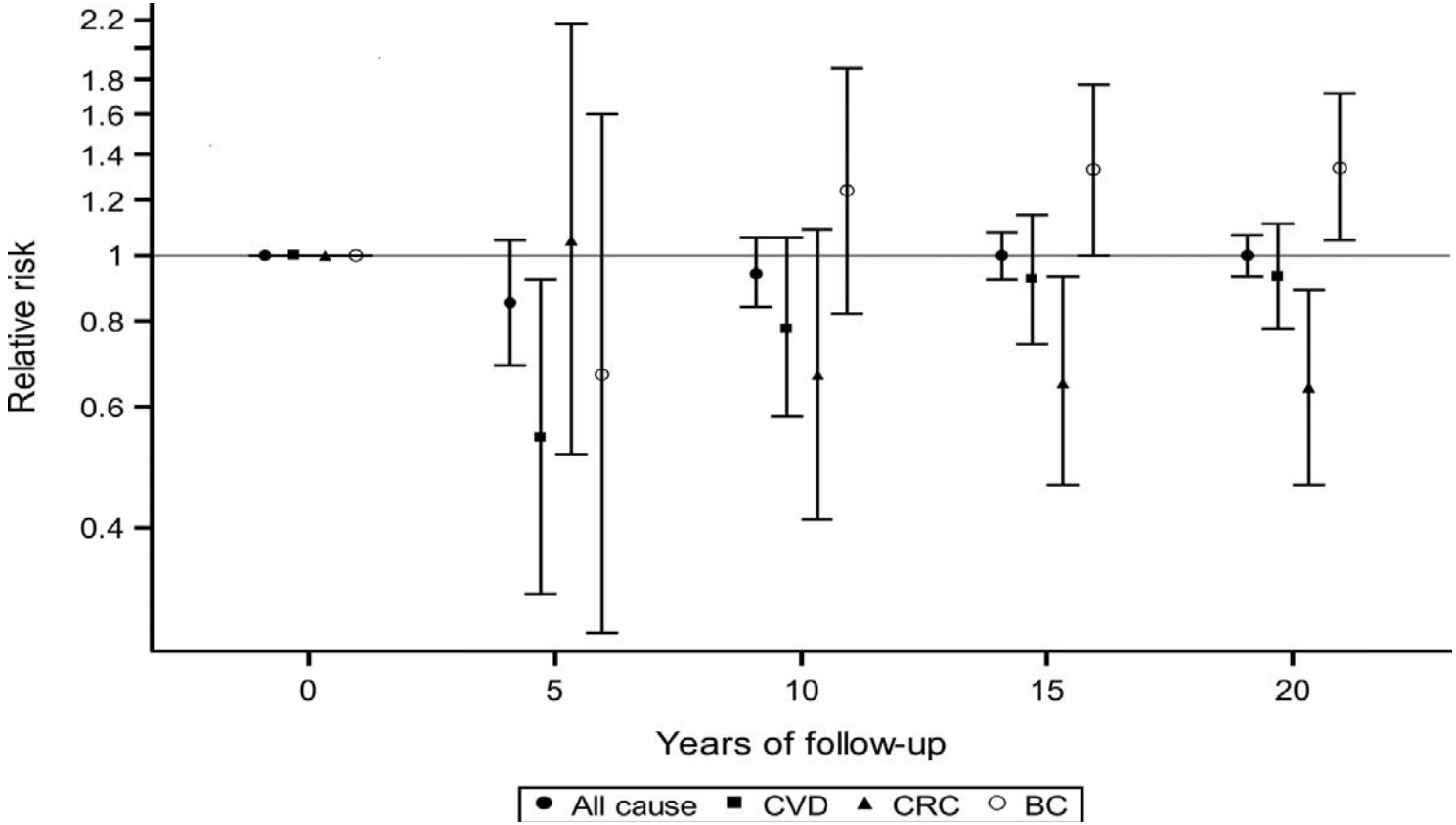

Figure 1. Development in adjusted mortality hazard ratios during follow up by selected causes of death in current versus never users of hormone

[a]adjusted for age (underlying timescale), alcohol, smoking, bmi, physical activity, and level of education; Follow up based on individual follow up time censored at 5-;10-;15-; and 20 years.
CVD (Cardiovascular disease); CRC (Colorectal cancer); BC (Breast cancer); Left axis: mortality HR