CANCER

Breast cancer incidence, case-fatality and breast cancer mortality in Danish women using hormone replacement therapy—a prospective observational study

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Accepted 19 April 2005

Keywords Hormone replacement therapy, breast neoplasm, prognosis, mortality, epidemiology, estrogen, progestin, menopause

It is well-established knowledge from both observational studies and randomized controlled trials that hormone replacement therapy (HRT) increases the risk of breast cancer.1−8 However, several studies have proposed that breast cancers developing in women using HRT may be more favourable with respect to one or more prognostic characteristics, implying that the prognosis may be better for breast cancers developing in women having used HRT before or at the time of diagnosis as compared with those of never users.9−17 A recent review of ten prospective cohort studies on breast cancer mortality showed both increased and reduced risk estimates of breast cancer mortality with HRT.18 A Danish study on breast cancer incidence and mortality according to social class showed increased mortality from breast cancer as well as increased incidence throughout higher social classes.19 More recently the Million Women’s Study found a 22% increased risk of breast cancer mortality in users of HRT.2 Several studies have reported reduced all-cause mortality among HRT users. It has been widely discussed that these findings could be explained by a selection of healthy women using HRT.20 The randomized controlled WHI study did not find any difference in all-cause mortality between the hormone and the placebo group.21

We have previously reported on the increased incidence of breast cancer with the use of HRT, and the risk of developing both prognostic favourable and non-favourable types of breast cancer.7,17 To evaluate the true possible hazardous effect of HRT, however, analyses of not only case-fatality but also the net effect on breast cancer mortality are most needed, as interpreting only case-fatality analyses might be misleading for both women and their physicians when evaluating the pros and cons of initiating or maintaining the use of HRT.

We, therefore, found it important to investigate the net effect of HRT, which forms a combined analysis of incidence, prognosis, breast cancer mortality, and all-cause mortality in a population of natural post-menopausal women with an intact uterus and without prior cancer disease.

Materials and Methods

The setting of this prospective cohort on breast cancer incidence following the use of HRT in Danish nurses has been described in detail previously.7,17 In summary, the Danish Nurse Cohort was established in 1993, when all female Danish nurses aged 44 years received a mailed questionnaire. A total of 19,898 women returned the questionnaire (86%). The mailed questionnaire of 1993 served as baseline information and included details on the use of HRT and potential confounders. Breast cancer cases were identified by linkage through the unique personal identification number to the Danish nationwide registries. The follow-up for incident cases started with the questionnaire in 1993, and ended December 31, 1999, while follow-up for death ended April 19, 2004.

All identified cases of breast cancer, CIS of the breast, and other invasive cancers except non-melanoma skin cancer (n = 1086) were excluded at baseline. Furthermore, women with missing information on HRT (n = 267), premenopausal women (n = 5084), and women with a surgical menopause (n = 571) were excluded. Finally, hysterectomized women (n = 2016) were excluded, leaving a total of 10,874 women for follow-up and analysis. More than one exclusion criterion was
fulfilled for several women. Data on prognostic characteristics were available from the Danish Breast Cancer Cooperative Group (DBCG) register as described in detail previously. The data on mortality were available from the Danish Civil Registration. The cause of death was retrieved from the National Causes of Death Register, but could not be ascertained for all women, owing to delay in registration procedure. Therefore, deaths in women with a breast cancer diagnosis were treated as breast cancer deaths. In 32 cases, we were able to cross-check with the National Causes of Death Register and the cause of death was breast cancer in all women, but one, who had committed suicide. Women were considered post-menopausal if the menstrual bleeding had ceased, or they were currently using HRT. Menopausal age was defined as the age at cessation of menstrual bleedings, or start of HRT—whichever came first.

The conditional Cox Proportional Hazards Model for left-truncated and right-censored data was used in the modelling of time-to-cancer-prognostic-factor and time-to-death outcomes. The nurse’s age was used as an underlying time with the age at study-entry as the delayed entry time in the analysis. Women with other histologies than invasive ductal carcinomas were censored at time of breast cancer diagnosis as well as breast cancers with missing information on one of the prognostic characteristics. The favourable and non-favourable breast cancers as two competing risks of each prognostic factor were considered as the endpoints. In addition, breast cancer case fatality, breast cancer mortality and all-cause mortality were considered. The case-fatality analysis (breast cancer case prognosis) was performed following the 244 breast cancer cases from the time of diagnosis as the entry date until death (case), or until the end of follow-up April 19, 2004 (right censoring). The effect of each of the prognostic factors on breast cancer survival was modelled separately. The breast cancer mortality analysis was performed by following the entire study population of 10 874 women until death or end of follow-up by April 19, 2004 (right censoring). Deaths among the 244 breast cancer cases were considered breast cancer deaths. The all-cause mortality analysis was based on the entire study population of 10 874 women with follow-up until death or end of follow-up by April 19, 2004. The first step in the analyses was modelling the outcome of interest univariately, with the HRT-exposure variable, unadjusted for confounders (except age, which is the delayed entry variable) and estimating the Hazard Ratios (HRs) and their 95% confidence intervals (CI). In the second step, each prognostic factor and mortality outcome was modelled in a multivariable Cox PH model, where HRs and their 95% CI were estimated for the HRT-exposure variable, adjusted for significant risk factors (smoking, alcohol use, body mass index (BMI), and physical activity). The proportional hazard assumption was checked for each Cox model. The analysis was performed in Stata version 7.0.

Results

In this population of 10 874 natural post-menopausal women, a total of 2726 women (25.1%) were current users of HRT, 1582 women were past users (14.5%), and 6566 women were never users of HRT at baseline in 1993.

A total of 244 women subsequently developed invasive breast cancer during the observation period from baseline in 1993 until December 31, 1999. Histological information was complete for 230 women: 172 developed invasive ductal carcinomas (74.8%), 36 were lobular tumours (15.6%), and 22 developed ‘other histologies’ such as mucinous, medullary, tubullary, and others (9.6%). A total of 71 among the 244 women diagnosed with breast cancer after baseline died before April 19, 2004. Case-fatality analysis according to the use of HRT showed a better prognosis in users of HRT as compared with never users, although not statistically significant; age-adjusted HR 0.77 (0.44–1.33). Breast cancer mortality was increased 2-fold in current users of HRT compared with never users, with HR 1.97 (1.14–3.42). The estimates are age-adjusted only, as they are based on a relatively small number of deaths and multiple adjusting would not be justified (Table 1).

Analysis of all-cause mortality was based on a total of 1225 deaths among 10 874 women. There was no influence of HRT on all-cause mortality; HR of 0.98 (0.83–1.16). Additional adjusting for smoking, physical activity, and alcohol use had only little effect on the estimate; HR 0.92 (0.77–1.10) (Table 2). The main findings have been summarized in Figure 1.

Analyses of the prognostic effect (case-fatality rate) of the different types of breast cancer showed significant decreased risks of dying from the prognostic favourable type of breast cancer compared with the non-favourable type, i.e. hormone receptor positive vs receptor negative breast cancer (RR 0.43 CI 0.22–0.82), low vs high histological malignancy grade (RR 0.24 CI 0.09–0.62), negative vs positive lymph node status (RR 0.33 CI 0.17–0.63), small vs large tumour size (RR 0.50 CI 0.27–0.92) and low vs high TNM stage (RR 0.11 CI 0.11–0.62).

Discussion

Recently we have reported an increased incidence of breast cancer in Danish women using HRT as compared with never users. The risk of developing both favourable and non-favourable prognostic types of breast cancer is increased 2 to 4-fold in current users of HRT as compared with never/past users, except for hormone receptor negative tumours.

Table 1 Use of HRT and breast cancer incidence, breast cancer case-fatality and breast cancer mortality

<table>
<thead>
<tr>
<th>HRT use (n)</th>
<th>Breast cancer incidence&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Case fatality&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Breast cancer mortality&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study population n = 10 874</td>
<td>No. of cases 244 cases/n = 10 874</td>
<td>No. of deaths (n = 71)</td>
<td></td>
</tr>
<tr>
<td>Never (6566)</td>
<td>110</td>
<td>1.00 (95% CI)</td>
<td>37</td>
</tr>
<tr>
<td>Past (1582)</td>
<td>31</td>
<td>1.16 (0.76–1.77)</td>
<td>12</td>
</tr>
<tr>
<td>Current (2726)</td>
<td>103</td>
<td>2.42 (1.81–3.26)</td>
<td>22</td>
</tr>
</tbody>
</table>

<sup>a</sup>Multivariate adjusted; <sup>b</sup>Age-adjusted.
with hormone receptor negative breast cancers. In current users of HRT, the incidence of different prognostic types of breast cancer was equally increased for the favourable and non-favourable types, except for hormone receptor status, where there was no increased risk of being diagnosed with a hormone receptor negative breast cancer, whereas the incidence of being diagnosed with a receptor positive breast cancer was increased 3-fold. Histological malignancy grade and hormone receptor status are biological variables and reflect a biological effect of HRT on tumour biology, whereas tumour size, lymph node status, and TNM stage represent time-dependent variables, which are more sensitive to detection bias. Other recent studies have supported our findings that women using HRT are at increased risk of developing hormone receptor positive breast cancer. These finding could explain the lower case-fatality rate among women currently using HRT. However, breast cancer mortality was increased 2-fold in current users of HRT, which reflects the effect of the increased incidence with the use of HRT and the net effect of HRT thus is a 2-fold increased risk of breast cancer mortality in hormone users, as compared with never users. As breast cancer incidence is increased for different prognostic types of breast cancer in users of HRT, the prognostic favourable effect of one of the biological variables, for instance, no increased risk of hormone receptor negative breast cancer, would have to be very strong to result in decreased breast cancer mortality.

Overall, mortality analyses showed no differential effect in users of HRT, which can be explained in two ways. Either HRT has some favourable effect on other causes of deaths, or the use of HRT is simply not related to other causes of death.

Nanda et al. recently reviewed 10 observational studies on breast cancer mortality with the use of HRT. The risk estimates for breast cancer mortality ranged from 0.48 to 1.89, where most studies showed a 20–30% reduction in breast cancer mortality, however, only statistically significantly so in two studies. Two other studies showed increased risk estimates by 80–90% but neither of these were statistically significant and CIs were wide. Four studies showed attenuation of the protective effect with increased duration of use, duration of follow-up, or years since use, thus analysing different aspects of HRT use and follow-up. Some studies included the effect of duration of HRT use, and others mainly duration of follow-up. Summary conclusions are thus difficult to obtain. Furthermore, the decreased breast cancer mortality observed in some observational studies could be explained by surveillance bias and the decreased all-cause mortality by the healthy user effect. Furthermore, the radiographic detection of breast cancers in women using HRT might be more difficult because of more

Breast cancer mortality refers to the a priori risk of dying from breast cancer for all women in the entire study population, while the prognosis estimated as the case-fatality rate refers to the risk of dying from breast cancer once diagnosed with the disease. In the present analysis, these two risk estimates work in opposite directions. After nearly 11 years of follow-up, case-fatality was reduced by 20% in current users of HRT compared with never users, although not statistically significant. The different prognostic types of breast cancer work in the anticipated directions in terms of case-fatality in this cohort, as women diagnosed with, for example, hormone receptor positive breast cancers experience better prognosis than women

### Table 2 Use of HRT and all-cause mortality

<table>
<thead>
<tr>
<th>HRT use (n)</th>
<th>No. of deaths</th>
<th>Mortality age-adjusted</th>
<th>Mortality multivariate adjusted</th>
</tr>
</thead>
</table>
| Study population | n = 10 874 | n = 1225 | HR (95% CI) | HR (95% CI)
| Never (6566) | 836 | 1.00 | 1.00 |
| Past (1582) | 200 | 1.03 (0.88–1.20) | 0.96 (0.81–1.14) |
| Current (2726) | 189 | 0.98 (0.83–1.16) | 0.92 (0.77–1.10) |

*Adjusted for: age, smoking, and physical activity.

**Figure 1** Breast cancer incidence, case-fatality, breast cancer mortality and all-cause mortality in current users of HRT as compared with never users
dense mammograms resulting in a higher false negative rate in mammographic screening rounds.21,22

Supportive of our findings, are the results from the Million Women’s Study, where an increased risk of breast cancer mortality was reported in users of HRT, with RR 1.22 (1.05–1.41).2 Follow-up time, however, was very short with a maximum of 4 years. The report on non-cardiovascular outcomes from the randomized HERS2 trial showed a 17% non-significant increase in cancer mortality, but based on only three cases of deaths from breast cancer occurring in the HRT group.23 A Swedish cohort study, found that despite a lower rate of cardiovascular deaths, the overall mortality rate in HRT users was neutral. As breast cancer incidence was increased, the authors suggested that an increased mortality from breast cancer might affect the overall outcome but no specific mortality rate for breast cancer was given.24 A randomized Scandinavian trial evaluating whether the use of HRT would be safe in women previously diagnosed with breast cancer was recently stopped prematurely because of an unacceptable high risk of recurrence in women exposed to HRT RR 3.5 (1.5–8.1) and in women exposed to HRT both before and after randomization RR 6.9 (1.6–31.1).25 Follow-up was relatively short with 5 years, and five women died in the HRT group as compared with four women in the placebo group. Analysis of different breast cancer characteristics and mortality was not possible. However, exposure effects and cancer development might be different in women where the process of carcinogenic effects leading to the development of cancer has already taken place once. It seems that both observational and randomized studies lack observation time to firmly establish any conclusion with respect to the long-term effect of HRT-use on breast cancer mortality.

Our analyses demonstrate the importance of analysing breast cancer morbidity and mortality in the entire study population and not restricting analysis to case-fatality, as too many previous studies have done.26–28 Our study has some limitations. In the present study, all deaths occurring in women with breast cancer were treated as breast cancer deaths. This approach will overestimate the true breast cancer deaths. However, this is not considered to be different for users or never users of HRT, and unlikely to explain the 2-fold observed difference. Furthermore, we were not able to control for possible confounding factors, as the number of deaths was small. The overall estimate of mortality from all causes based on 1225 deaths hardly changed with the multivariate adjusting, indicating that the crude age-adjusted mortality figure was stable. Our study does not support the notion that breast cancer mortality is reduced in HRT users, but on the contrary suggests that mortality is increased after 11 years of follow-up. A longer follow-up period though, is needed before firm conclusions on breast cancer mortality can be drawn.

In conclusion, numerous studies have shown an increased risk of breast cancer following the use of HRT. Long-term treatment with HRT leaves more women not only with a breast cancer, but also possible side effects following medical and surgical treatment. Our study finds that despite a better prognosis in women diagnosed with breast cancer (case-fatality), breast cancer mortality is increased in users of HRT as compared with never users. Further studies with a longer follow-up time are needed to confirm these findings. However, the possibility of not only increased incidence, but also increased mortality from breast cancer should be taken into account when counselling menopausal women in their choice of using HRT.

Acknowledgements
The present study has been sponsored by The Danish Cancer Society, the ‘Erland Frederiksen og Hustrus’s foundation’.

Ethical approval
The Scientific and Ethical Committee of Frederiksberg and Copenhagen has approved the Danish Nurse Cohort including analyses in the present study (KF 11-035/00). The Danish Data Protection Agency has been notified and had no objections with respect to access to the Danish Cancer Registry, the Danish Breast Cancer Group’s registry and National Registry of Hospital admissions and discharges (2001-54-0860). Data are kept by the National Institute of Public Health, Copenhagen.

Conflicts of interest
B.O. and A.T.P., having an interest in HRT, have been reimbursed by different pharmaceutical industries for speaking at conferences and workshops. The Danish Nurse Cohort has, among others, received financial support by grants from different pharmaceutical industries for costs related to distribution of questionnaires and the handling of data.

KEY MESSAGES
• The net effect of HRT on breast cancer mortality is a 2-fold increased risk among users compared with never users.
• Once being diagnosed with breast cancer, hormone users experience a better prognosis compared with never users of HRT, with a lower case-fatality rate.
• The lower case-fatality rate is counterbalanced by the increased incidence of breast cancer with the use of HRT, the net effect being an increased mortality.
• Risk assessment should focus on the net effect of HRT on breast cancer combining incidence, case-fatality, and mortality.
References


