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Lifestyle influences on the association between pre-diagnostic hormone replacement therapy and breast cancer prognosis—Results from The Danish 'Diet, Cancer and Health' prospective cohort

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ABSTRACT

Objectives: The association between pre-diagnostic hormone replacement therapy (HRT) and breast cancer specific mortality as well as potential influences from other lifestyle factors on the association was investigated.
Study design: Female participants from the prospective cohort "Diet, Cancer, and Health" diagnosed with breast cancer (BC) were identified and their pre-diagnostic HRT use evaluated for association with tumour biology and breast cancer outcome in multivariate analysis.
Main outcome measure: Breast cancer specific mortality.
Results: Of the 1212 patients originally considered 1064 were included. Of these, 105 women died from breast cancer during a median follow-up of 6.3 years (range 0.2–14.3 years). In multivariate analyses women who used HRT at enrolment into the cohort study had 47% lower risk of dying from breast cancer as compared to women who had previously or never used HRT (adjusted HR: 0.53; 95% CI, 0.37–0.85). Pre-diagnostic HRT use was associated with smaller tumour size at the time of diagnosis and a higher frequency of receptor positive breast cancer. Paradoxically, a high pre-diagnostic intake of vitamin D supplements was associated with HRT use but also with a higher BC specific mortality (HR: 1.47; 95% CI, 1.07–2.00)
Conclusions: HRT use at enrolment was associated with breast tumours of smaller size at the time of diagnosis and positive receptor status, and with a lower BC mortality. The found association between vitamin D from supplements and higher BC mortality warrants further exploration.

1. Introduction

Hormone replacement therapy (HRT) is an established risk factor for breast cancer (BC) [1,2], however a preponderance of observational studies have reported pre-diagnostic HRT use to be associated with a better prognosis, and mainly attributed this to more favourable tumour characteristics [3–9].

In contrast to these pretty consistent findings from observational studies the Women's Health Initiative (WHI) randomized controlled trial (RCT) of HRT versus placebo found that tumours that developed in women who were randomized to receive HRT were of a more advanced stage (i.e. higher frequency of lymph node positive tumours) compared to the ones in the placebo group [2], and a recent follow-up from the study showed a borderline significantly increased risk of dying from breast cancer in the treated group [10]. An observational study correlated to the WHI-RCT found the prognosis of HRT users similar to that of non-users [11].

Several attempts at explaining both the differential effect of HRT on BC pre- and post-diagnosis as well as the conflicting findings have been made [12]. Among these is the argument that the better survival among HRT users seen in observational studies can be explained by increased surveillance of women using HRT and consequently earlier diagnosis [12,13]. However, several of the more recent observational studies have attempted to adjust for the postulated higher screening among HRT users and still found a superior prognosis beyond what could be attributed to increased screening [3,4,9], although not all of them [14,15].

Abbreviations: HRT, hormone replacement therapy; BMI, body mass index.

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Recently, more interest has gone into studying possible interactions in the association between HRT use and breast cancer outcome. Reding et al. found that the reduced risk was mainly confined to older women (>65 years) [9], and Rosenberg et al. found BMI to be associated with a poor prognosis only in HRT users [16]. Another study found the duration of HRT use to have an impact on the direction of the association between pre-diagnostic use and prognosis [14]. As a large proportion of the women participating in the WHI trial were also randomized to receive vitamin D supplement, and because interactions between HRT and vitamin D supplement on cancer risk have been suggested previously [17] this factor is relevant to examine as well.

With the large population based "Diet, Cancer, and Health" (DCH) cohort as starting point this study investigates the association between pre-diagnostic Hormone Replacement Therapy and breast cancer specific mortality as well as the possible influence of age, BMI, and use of vitamin D supplement on this relationship.

2. Methods

2.1. Study population

This study was conducted in the large population based 'Diet, Cancer and Health' (DCH) cohort. 29 875 women aged 50–64 (at time of enrolment) were included between 1993 and 1997. A detailed description of the cohort has been published previously [18]. Between enrolment and December 31st 2006, 1212 incident cases of breast cancer were diagnosed. These patients were included in the current study and followed up through December 31st 2008 for outcomes of breast cancer specific mortality.

2.2. Case ascertainment and follow-up

Breast cancer diagnosis was ascertained via linkage with the Danish Cancer Registry (linkage 99.8%) [19]. Breast cancer patients with carcinoma in situ of the breast ($n = 41$) or advanced disease (distant metastatic spread) ($n = 10$) at the time of diagnosis were excluded from the study. The participants entered into the study from the date of their breast cancer diagnosis and were followed-up until either: date of death, date of emigration, or end of follow-up. Participants who had missing information on exposure ($n = 2$), or covariates ($n = 95$) were excluded, leaving 1064 patients in the final analyses, see Fig. 1.

2.3. Outcomes and exposure

The chosen prognostic outcome was breast cancer specific mortality, which was ascertained via linkage with The Danish Causes of Death registry [20], the follow-up on this outcome was complete (100%).

Pre-diagnostic use of HRT was the primary exposure of interest. Exposure was measured at enrolment into study with a self-administered, interviewer-checked lifestyle questionnaire, where the participants answered questions about their use of HRT, whether 'never', 'previous', or 'current', and, if applicable, the age at which they started taking HRT, as well as the duration of the intake. Two exposure variables were chosen for the current study: HRT use as a binary variable categorized as 'current users' vs 'previous and never users' and HRT duration categorized into <5 years and ≥5 years, and also a duration measure where current users were divided into 'short term' (<5 years) and 'long term' (≥5 years) users. This binary categorization was chosen to ease comparison with other studies in which this was the most frequent cut off-point reported.

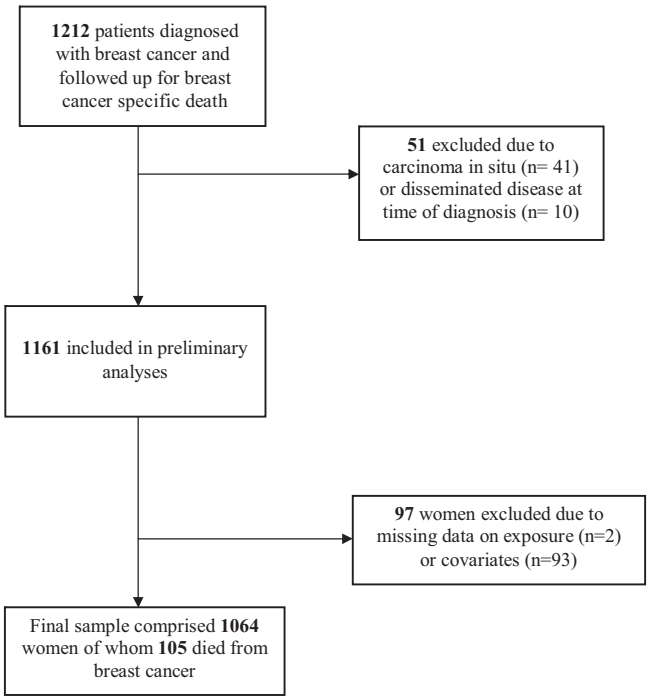

Fig. 1. Overview of Diet, Cancer, and Health cohort participants diagnosed with breast cancer and included in the study; outlining number of patients excluded due to pre-set exclusion criteria or due to missing data.

2.4. Covariates

Two different types of covariates were considered for this study: (1) tumour characteristics that are established important prognostic determinants in breast cancer patients, and (2) other covariates that by à priori hypothesis were suspected to influence the association between HRT use and breast cancer prognosis. The latter ones were: age at diagnosis, BMI, and vitamin D supplement intake.

2.4.1. Tumour characteristics

Information on tumour characteristics was obtained from the Danish Breast Cancer Cooperative Group database (DBCG) and included tumour size, number of axillary lymph nodes with breast cancer metastases, and tumour oestrogen and progesterone receptor status. DBCG is a national registry with information on more than 95% of all diagnosed cases of breast cancer in Denmark [21]. Tumour size and lymph node status were analyzed both as continuous and categorical variables, the categories were chosen according to the levels used when classifying breast cancers according to TNM stage [22]: 'tumour size': <1 mm; ≥1 mm to <5 mm; ≥5 mm to <10 mm; ≥10 to <50 mm; >50 mm, 'number of positive lymph nodes': 0; 1–3; 4–10; >10. Receptor status was combined for both oestrogen and progesterone receptors and designated hormone receptor 'positive' versus 'negative'.

2.4.2. Other covariates

At enrolment into the DCH study the participants' height and weight were measured by a lab technician and BMI was calculated. In this study the BMI variable was analyzed both as a continuous and categorical measure (<20; 20 to <25; 25 to <30; >30). Age was treated similarly with category limits chosen at the 25-, 50-, and 75-percentiles of the age distribution (<58 years; 58 to <62 years; 62 to <66 years; >66 years).