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ARTICLE

Mortality and Risk of Cancer After Prophylactic Bilateral Oophorectomy in Women With a Family History of Cancer

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Abstract

Background: Current international guidelines recommend systemic hormone therapy (HT) to oophorectomized women until the age of natural menopause. Despite an inherited predisposition to estrogen-dependent malignancies, the guidelines also apply to women oophorectomized because of a family history of cancer. The objective of this study was to investigate the impact of HT on mortality and risk of cancer in women oophorectomized because of a family history of cancer.
Methods: A nationwide, population-based cohort was used to study women oophorectomized because of a family history of cancer (n = 2002). Comparison cohorts included women from the background population individually matched on age (n = 18 018). Oophorectomized women were subdivided into three groups: oophorectomized at 1) age 45 years or younger not using HT, 2) age 45 years or younger using HT, 3) older than age 45 years, and their respective population comparison cohorts.
Results: Women oophorectomized at age 45 years or younger using HT had increased overall mortality (mortality rate ratio [MRR] = 3.45, 95% confidence interval [CI] = 1.53 to 7.79), mortality because of cancer (MRR = 5.67, 95% CI = 1.86 to 17.34), and risk of overall cancer (incidence rate ratio [IRR] = 3.68, 95% CI = 1.93 – 6.98), primarily reflected in an increased risk of breast cancer (IRR = 4.88, 95% CI = 2.19 – 10.68). Women oophorectomized at age 45 years or younger not using HT and women oophorectomized at older than age 45 years did not have increased mortality, mortality because of cancer, or risk of overall cancer, but they had increased risk of breast cancer (IRR = 2.64, 95% CI = 1.14 to 6.13, and IRR = 1.72, 95% CI = 1.14 to 2.59, respectively).
Conclusions: Use of HT in women oophorectomized at age 45 years or younger with a family history of cancer is associated with increased mortality and risk of overall cancer and breast cancer. Our study warrants further investigation to establish the impact of HT on mortality and cancer risk in oophorectomized women with a family history of cancer.

The cumulative lifetime risks of ovarian and breast cancer among Danish women are approximately 1% and 10%, respectively (1). Germline mutations in BRCA 1 or 2 genes increase breast, ovarian, and overall cancer risks considerably and are associated with diagnosis at a young age (2,3). Bilateral oophorectomy performed before natural menopause reduces the risk of cancer substantially (4–9) but may impair cognition (10) and increase the risk of cardiovascular disease (8,11) and all-cause mortality (8,11,12). An immediate side effect of bilateral oophorectomy in premenopausal women is the induction of surgical menopause, often associated with vasomotor symptoms and reduced quality of life (13), which can be avoided through the use of hormone therapy (HT) (14). At the same time, HT has been hypothesized to reduce morbidity and mortality in women with a history of bilateral oophorectomy (12).

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Although observational studies have shown that the use of hormone therapy after natural menopause, regardless of regimen, is associated with an increased risk of breast cancer (15,16), randomized controlled trials have only found progestin-containing HT to be associated with increased risk of breast cancer (17–20), and estrogen-only HT has been associated with no (21) or even a decreased (19,20,22) breast cancer risk.

Previous studies in humans and rodents have indicated that end organ hormone sensitivity is increased in BRCA mutations carriers, which could potentially affect hormones' influence on cancer risk in this group of women (23,24). Few studies have investigated the association between HT and cancer risk, morbidity, and mortality in women oophorectomized because of inherited predisposition for estrogen-dependent cancers, and the studies lack information on HT regimens (25–27), are mainly performed in case–control designs with no representative control cohorts (25–27), and are hampered by small study populations (25–27). Although the evidence is limited (25–27), current international guidelines (28) recommend systemic HT from the time of bilateral oophorectomy until the age of natural menopause despite an inherited predisposition for estrogen-dependent cancers.

We used a nationwide population-based cohort design to compare mortality, risk of cancer, and comorbidity among women oophorectomized because of a family history of cancer with that of an age- and sex-matched population comparison cohort. We further analyzed the impact of HT on the outcomes of interest in women oophorectomized at age 45 years or younger.

Methods

Setting

In 2015, Denmark's adult female population consisted of 2.2 million women (29). Throughout the study period, tax-supported medical care was provided free of charge to all Danish residents. A unique 10-digit personal identification number (30) assigned to all Danish citizens at birth or upon immigration permits cross-linkage between national registers on an individual level. We used this PIN to avoid multiple registrations and to track individuals in Danish national health registries (Supplementary Materials, available online).

Cohort of Oophorectomized Women

The cohort consisted of all women oophorectomized after age 20 years in Denmark between January 1, 1994, and April 1, 2015, with a simultaneous diagnosis of a family history of cancer. Date of prophylactic bilateral oophorectomy and family history of cancer were extracted from the National Patient Registry. Study inclusion was defined as one year after prophylactic bilateral oophorectomy. We excluded women who were diagnosed with cancer, emigrated, or died before study inclusion.

Population Comparison Cohort

For each individual in the cohort of oophorectomized women, we identified all Danish women with the same date of birth who had not been diagnosed with cancer or had not undergone bilateral oophorectomy based on a family history of cancer, emigrated, or died before study inclusion. From this cohort, we extracted nine individuals at random for each oophorectomized woman. Women in the population comparison cohort were assigned the same date of study inclusion as the oophorectomized woman to whom they were matched.

Outcomes

Outcomes were time to 1) death of any cause, 2) death because of cancer, 3) death not because of cancer, 4) diagnosis of overall cancer, 5) diagnosis of breast cancer, and 6) diagnosis of non-breast cancer. Furthermore, we analyzed time to a diagnosis of cardiovascular disease, low-energy fracture, and infections. Outcomes were extracted from the Danish national health registries (Supplementary Materials, available online).

Family History of Cancer

Family history of cancer was defined as having one or more of the following ICD-10 codes: family history of breast cancer (Z80.3; n = 1371, 68.5%), family history of genital cancer (Z80.4, Z84.2; n = 1530, 76.4%), family history of cancer with no specification (Z40.0, Z40.8, Z40.9Z, 80.8, Z80.9; n = 61, 3.0%), family history with a known genetic defect (Z84.8; n = 880, 44.0%).

Hormone Therapy

We defined HT users as women who redeemed at least two prescriptions of HT within the first year after oophorectomy. HT was defined by Anatomical Therapeutic Chemical Classification (ATC) codes including the following groups of pharmaceuticals: estrogen-only therapy (G03C) and progestin-containing HT (G02BA03, levonorgestrel intrauterine system [LNG-IUS], G03D, and G03F), excluding all locally vaginally applied preparations. Women who had an LNG-IUS applied up to five years before study inclusion who were not hysterectomized were included in the progestin-containing HT group (Supplementary Figure 3, available online).

Statistical Analyses

In time-to-event analyses, time was calculated from study inclusion to date of emigration or death, loss to follow-up, April 1, 2016, 10 years after study inclusion, or outcome of interest, whichever came first. In analyses of time to breast cancer, time was censored at the date of prophylactic bilateral mastectomy. Observation time was censored at 10 years, as the numbers at risk after this time point were limited.

To estimate all-cause mortality, we used the Kaplan-Meier estimator. To estimate incidence of other events of interest, we used the cumulative incidence function with death (and for breast cancer, date of bilateral mastectomy) as competing risks. We used Cox regression to calculate unadjusted and adjusted mortality rate ratios (MRRs) and incidence rate ratios (IRRs) and controlled for Charlson Comorbidity Index (CCI; 0/>0), educational level (above/below high school), and native Danish (yes/no), with 95% confidence intervals (CIs) as estimates of relative risk.

For each year starting 10 years before date of study inclusion, immigration, or start of the Danish National Prescription Registry until end of the study, we ascertained the redemption of HT in each woman oophorectomized at age 45 years or younger (Supplementary Figure 4.1, available online). For women oophorectomized at age 45 years or younger, we calculated date

Table 1. Characteristics of women oophorectomized because of a family history of cancer and members of the population comparison cohort, Denmark, 1994–2016

Characteristics	Women oophorectomized ≤45 y – HT	Population comparison cohort	Women oophorectomized ≤45 y + HT	Population comparison cohort	Women oophorectomized >45 y	Population comparison cohort
Total, No.	302	2718	564	5076	1136	10 224
Age at study inclusion, median (IQR), y	42 (39–44)	42 (39–44)	40 (37–42)	40 (37–42)	51 (48–57)	51 (48–57)
Born in Denmark, No. (%)	293 (97.0)	2397 (88.2)	551 (97.7)	4395 (86.6)	1097 (96.6)	9363 (91.6)
Bilateral mastectomized, No. (%)*	8 (2.6)	0 (0.0)	57 (10.1)	1 (0.0)	21 (1.9)	2 (0.0)
Hysterectomized, No. (%)*	80 (26.5)	72 (2.6)	267 (47.3)	89 (1.8)	359 (31.6)	532 (5.2)
Charlson Comorbidity Index score >0, No. (%)*,†	36 (11.9)	236 (8.7)	39 (6.9)	458 (9.0)	166 (14.6)	1538 (15.0)
Mean total observation time, y	1649	14 759	2577	23 299	5294	47 337
Observation time, median (IQR), y	6.2 (3.9–8.9)	6.2 (3.9–9.0)	5.1 (2.8–8.2)	5.1 (2.8–8.2)	5.3 (3.1–8.2)	5.2 (3.0–8.2)
Emigrated, No. (%)§	1 (0.3)	15 (0.6)	1 (0.0)	40 (0.8)	3 (0.3)	41 (0.4)
Lost to follow-up, No. (%)§	0 (0.0)	1 (0.0)	0 (0.0)	3 (0.0)	0 (0.0)	1 (0.0)
Obtained a high school or vocational education, No. (%)*	244 (81)	2131 (78)	484 (86)	4101 (81)	881 (78)	7129 (70)
Death, total, No. (%)§	1 (0.3)	16 (0.6)	8 (1.4)	21 (0.4)	18 (1.6)	229 (2.2)
Death, cancer, No. (%)§	1 (0.3)	7 (0.3)	5 (0.9)	8 (0.2)	8 (0.7)	70 (0.7)
Death, other causes, No. (%)§	0 (0.0)	9 (0.3)	3 (0.5)	13 (0.3)	10 (0.9)	159 (1.6)
Cancer, total, No. (%)§	7 (2.3)	63 (2.3)	24 (4.3)	70 (1.4)	57 (5.0)	432 (4.2)
Breast cancer, No. (%)§	7 (2.3)	24 (0.9)	16 (2.8)	36 (0.7)	27 (2.4)	142 (1.4)
Other cancers, No. (%)§	0 (0.0)	39 (1.4)	8 (1.4)	35 (0.7)	30 (2.6)	293 (2.9)
Bilateral mastectomized, No. (%)§	18 (6.0)	1 (0.0)	37 (6.6)	0 (0.0)	13 (1.1)	1 (0.0)

*Before study inclusion. HT = hormone therapy; IQR = interquartile range.
†A modified Charlson Comorbidity Index (CCI) score derived from diagnoses recorded in the Danish National Patient Registry at study inclusion. The CCI assigns a score to a range of comorbidities known to be predictive of mortality. For simplicity we dichotomized scores (CCI score = 0 and CCI score >0).
§Diagnosed after study inclusion.

to first exposure of HT and date to exposure of 730 defined daily doses (equivalent to two years of exposure) and introduced these two time-updated variables in a Poisson regression model to calculate overall cancer and breast cancer risk before, after short-term (less than two years), and after long-term (more than two years) HT exposure. These estimates were further adjusted for age (continuous variable) and calendar period (before 2006, 2006–2011, and after 2011) at study inclusion and at the start of each time interval.

To account for potential differences in comorbidity at the time of study inclusion, we calculated the fraction of individuals with a CCI greater than zero at study inclusion.

Differences in receptor expression between groups were tested with two-way analysis of variance (PROC GLM) in SAS 9.1 (SAS Institute, Cary, NC). Statistical analyses were done using IBM SPSS statistics, version 22, and R, version 3.4.0 (R Development Core Team, 2008, R Foundation for Statistical Computing, Vienna, Austria). Poisson regressions were conducted in STATA statistics, version 14.2.

The study was approved by the Danish Data Protection Agency (RH-2016-04). Ethics approval and individual consent are not required by Danish legislation governing this type of study.

Results

During the period from January 1, 1994, to April 1, 2015, we identified 3628 women oophorectomized after age 20 years with a diagnosis of a family history of cancer. Of the oophorectomized women, 1612 (44.4%) were diagnosed with cancer, 11 (0.5%) emigrated, and three died (0.1%) before study inclusion, leaving a total of 2002 oophorectomized women and 18 018 members of the population comparison cohort in the study (Table 1; Supplementary Appendix 2, available online). The final study population consisted of 302 women oophorectomized at age 45 years or younger – HT (median follow-up time [interquartile range {IQR}] = 6.2 [3.9–8.9] years), 564 women oophorectomized at age 45 years or younger + HT (median follow-up time [IQR] = 5.1 [2.8–8.2] years), 1136 women oophorectomized at older than age 45 years (median follow-up time [IQR] = 5.3 [3.1–8.2] years), and their respective population comparison cohorts (median follow-up times [IQR] = 6.2 [3.9–9.0] years, 5.1 [2.8–8.2] years, and 5.3 [3.0–8.2] years). Of the 564 women using HT, 319 (56.6%) used estrogen-only HT and 245 (43.4%) used progestin-containing HT.

Mortality

One woman oophorectomized at age 45 years or younger – HT died during the study period. We observed no increased mortality in women oophorectomized at age 45 years or younger – HT (MRR = 0.56, 95% CI = 0.07 to 4.22). Mortality was increased in women oophorectomized at age 45 years or younger + HT (MRR = 3.45, 95% CI = 1.53 to 7.79) but not in women oophorectomized at older than age 45 years (MRR = 0.70, 95% CI = 0.44 to 1.14) (Figure 1; Supplementary Table 4, available online). The increased mortality in women oophorectomized at age 45 years or younger + HT was caused by an increased mortality from cancer (MRR = 5.67, 95% CI = 1.86 to 17.34) (Supplementary Table 4, available online). We observed no substantial differences between unadjusted and adjusted estimates of mortality (data not shown).

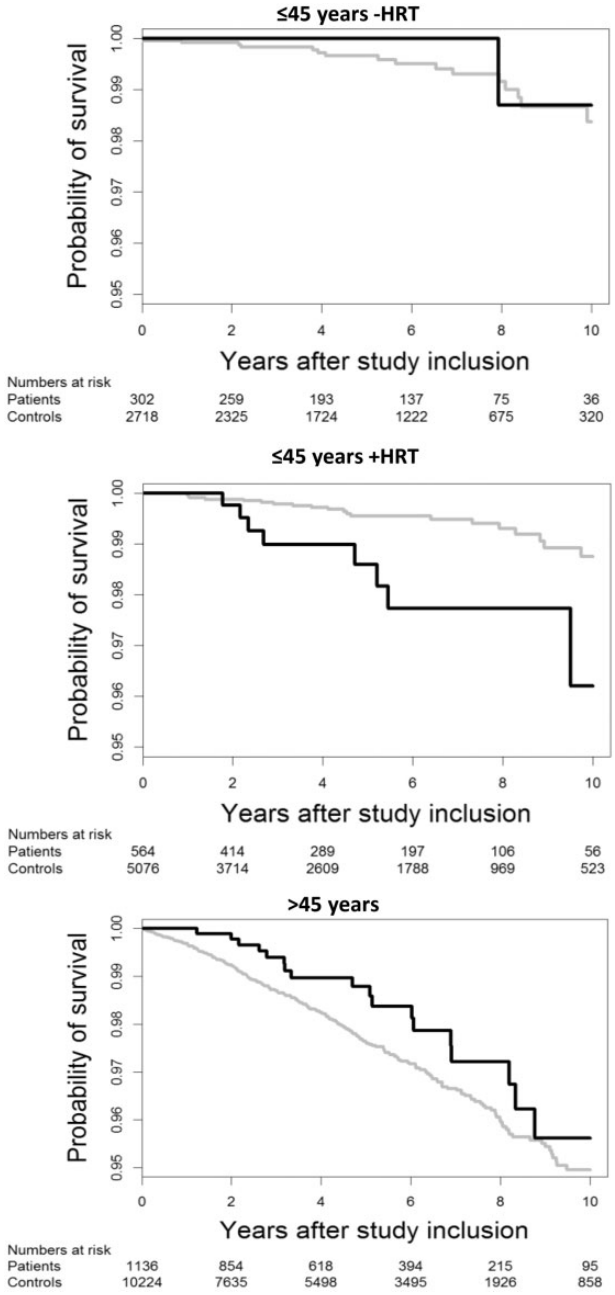

Figure 1. Survival after bilateral prophylactic oophorectomy. Probability of survival after prophylactic oophorectomy in 302 women oophorectomized at age 45 years or younger – hormone therapy (HT; **black**), 2718 individuals from the population comparison cohort (**gray**), 564 women oophorectomized at age 45 years or younger + HT (**black**), 5076 individuals from the population comparison cohort (**gray**), 1134 women oophorectomized at older than age 45 years (**black**), and 10 206 individuals from the population comparison cohort (**gray**).

Cancer Risk

Women were categorized as having cancer if they were registered with a diagnosis of cancer in either the Danish Cancer Registry or the Danish National Patient Registry; 94% of the cancer diagnoses were registered in both registries.

Women oophorectomized at age 45 years or younger – HT had no increased risk of overall cancer compared with the population comparison cohort (IRR = 1.00, 95% CI = 0.46 to 2.18). Overall cancer risk was increased in both women oophorectomized at age 45 years or younger + estrogen-only HT (IRR = 3.68, 95% CI = 1.93 to 6.98) and women oophorectomized at age 45 years or younger + progestin-containing HT (IRR = 2.72, 95% CI = 1.39 to 5.34) but not in women oophorectomized at older than age 45 years (IRR = 1.20, 95% CI = 0.91 to 1.58) (Table 2A, Figure 2). The increased risk of overall cancer in women oophorectomized at age 45 years or younger + HT was primarily reflected in an increased risk of breast cancer (estrogen-only HT: IRR = 4.88, 95% CI = 2.19 to 10.68) and progestin-containing HT (IRR = 4.70, 95% CI = 1.89 to 11.65). Yet, the risk of breast cancer was increased in all three study groups compared with the population comparison cohorts (women oophorectomized at age ≤45 years – HT: IRR = 2.64, 95% CI = 1.14 to 6.13) and women oophorectomized at older than age 45 years (IRR = 1.72, 95% CI = 1.14 to 2.59) (Table 2A, Figure 2).

Oophorectomized women were more likely to have estrogen receptor (ER)–negative breast cancer than the population comparison cohort ($P = .01$) (data not shown). HT or age at prophylactic oophorectomy did not affect ER status. There were no differences in human epidermal growth factor receptor 2 (HER2) expression of the breast cancers between the groups (data not shown).

We observed no increased risk of nonbreast cancers in any of the study groups (Figure 2C). There were no substantial differences between unadjusted and adjusted estimates of cancer risk (data not shown).

Cancer Risk and Time of HT Exposure

Up to two years of daily intake of estrogen-only HT was associated with increased risk of overall cancer (IRR = 2.54, 95% CI = 1.12 to 5.80) and breast cancer (IRR = 5.38, 95% CI = 2.12 to 13.61) compared with the population comparison cohorts. Up to two years of daily intake of progestin-containing HT was associated with increased risk of overall cancer (IRR = 3.10, 95% CI = 1.36 to 7.07) and breast cancer (IRR = 3.94, 95% CI = 1.22 to 12.71) compared with the population comparison cohort. More than two years of daily intake of estrogen-only HT was associated with increased risk of overall cancer (IRR = 2.37, 95% CI = 1.15 to 4.89) and breast cancer (IRR = 3.91, 95% CI = 1.53 to 9.96) compared with the population comparison cohort. More than two years of daily intake of progestin-containing HT was not associated with a significantly increased risk of overall cancer or breast cancer compared with the population comparison cohort (IRR = 1.25, 95% CI = 0.51 to 3.08, and IRR = 2.70, 95% CI = 0.95 to 7.61) (Table 3).

Noncancer Morbidity

None of the study groups had an increased incidence of cardiovascular disease compared with the population comparison cohorts (Table 2B; Supplementary Figure 5A, available online). Women oophorectomized at age 45 years or younger had an increased risk of low-energy fractures (IRR = 1.57, 95% CI = 1.03 to 2.41) compared with the population comparison cohort, and the risk was not substantially different between –HT and +HT women (Table 2B; Supplementary Figure 5B, available online). A similar increased risk of low-energy fractures was not observed in women oophorectomized at older than age 45 years (IRR = 0.90, 95% CI = 0.67 to 1.22). We found an increased risk of infections in women oophorectomized at age 45 years or younger (IRR = 1.29, 95% CI = 1.02 to 1.62) compared with the population comparison cohort, and the risk was not substantially different between –HT and +HT women. Women

Table 2A. Incidence rate ratios of cancers, in women oophorectomized because of a family history of cancer compared with members of the population comparison cohort, Denmark, 1994–2016*

	Women oophorectomized ≤45 y – HT vs population comparison controls	Women oophorectomized ≤45 y + estrogen-only HT vs population comparison controls	Women oophorectomized ≤45 y + progestin-containing HT vs population comparison controls	Women oophorectomized >45 y vs population comparison controls
	IRR (95% CI)	IRR (95% CI)	IRR (95% CI)	IRR (95% CI)
Overall cancer	1.00 (0.46 to 2.18)	3.68 (1.93 to 6.98)	2.72 (1.39 to 5.34)	1.20 (0.91 to 1.58)
Breast cancer	2.64 (1.14 to 6.13)	4.88 (2.19 to 10.68)	4.70 (1.89 to 11.65)	1.72 (1.14 to 2.59)
Nonbreast cancer	No incidents in oophorec-tomized women	2.62 (0.68 to 7.95)	0.68 (0.24 to 1.88)	0.92 (0.63 to 1.34)

*CI = confidence interval; HT = hormone therapy; IRR = incidence rate ratio.

Table 2B. Incidence rate ratios of cardiovascular disease, low-energy fractures and infections in women oophorectomized because of a family history of cancer compared with members of the population comparison cohort, Denmark, 1994–2016*

	Women oophorectomized ≤45 y – HT vs population comparison controls IRR (95% CI)	Women oophorectomized ≤45 y + HT vs population comparison controls IRR (95% CI)	All women oophorectomized ≤45 y vs population comparison controls IRR (95% CI)	Women oophorectomized >45 y vs population comparison controls IRR (95% CI)
Cardio vascular disease	0.81 (0.45 to 1.47)	0.83 (0.50 to 1.36)	0.82 (0.56 to 1.20)	0.94 (0.77 to 1.16)
Low-energy fractures	1.48 (0.78 to 2.81)	1.65 (0.93 to 2.91)	1.57 (1.03 to 2.41)	0.90 (0.67 to 1.22)
Infections	1.23 (0.85 to 1.80)	1.32 (0.99 to 1.78)	1.29 (1.02 to 1.62)	1.05 (0.85 to 1.30)

*CI = confidence interval; HT = hormone therapy; IRR = incidence rate ratio.

oophorectomized at older than age 45 years had no increased risk of infections (IRR = 1.05, 95% CI = 0.85 to 1.30) (Table 2B; Supplementary Figure 5C, available online). We observed no substantial difference between unadjusted and adjusted estimates of risk of cardiovascular disease, low-energy fractures, or infections (data not shown).

Discussion

We conducted a large nationwide population-based cohort study of women oophorectomized because of a family history of cancer in Denmark between January 1, 1994, and April 1, 2015.

We found that women oophorectomized at age 45 years or younger + HT had an increased mortality and risk of overall cancer, primarily reflected in an increased risk of breast cancer. All regimens of HT were associated with an increased cancer risk.

In contrast to our findings, Rocca and colleagues (12) found that only oophorectomized women not using HT to age 45 years had an increased mortality. However, they did not include HT as a time-updated variable and thereby might have underestimated the mortality in the group taking HT. To avoid immortal time bias, we categorized HT users from data available before study inclusion or included HT use as a time-updated variable. The differences seen in effect of HT on mortality could also be due to different effects of HT in women oophorectomized because of increased risk of estrogen-dependent cancers and women oophorectomized for other causes. In this study, there was a low number of fatal events in women oophorectomized at age 45 years or younger, affecting the precision of the risk estimates.

A key finding in this study was an increased risk of overall cancer in women oophorectomized at age 45 years or younger + HT. This is in contrast to previous studies (25–27) reporting no effect of HT on cancer risk after prophylactic oophorectomy. These studies obtained HT information from interviews and recall from the women, whereas our information was based on the Danish National Prescription Registry. With this design, we avoided recall bias.

Vaginally applied HT preparations have been shown to have only local effects not related to increased cancer morbidity or mortality (31,32), which is why they were excluded in our definition of HT. All former studies presumably included vaginally applied hormones as HT, and these less potent hormone preparations could potentially minimize the effect of HT on cancer risk.

Previous studies (25–27) investigating the effects of HT in women predisposed to cancer reported an average use of HT of 2.4 to 4.3 years. We defined two different levels of exposure to HT as less than two years of daily HT and more than two years of daily HT and calculated the risk of overall cancer and breast cancer during the different exposure periods. We found that both short- and long-term HT exposures were associated with an increased risk of overall cancer and breast cancer. However, the cancer risk seemed to be highest early in the HT exposure period. The rapid increase in breast cancer risk after initiation of HT could indicate that a fraction of the oophorectomized women have subclinical breast cancers at the time of HT initiation and the growth of these tumors is promoted by exposure to HT (33).

The increased cancer risk with HT in postmenopausal women depends on the type of preparations and regimens (15–18). Thus, the intake of estrogen combined with progestin has been associated with a marked increase in breast cancer risk in both observational (15,16,18,34) and randomized controlled trials (17,19,20), whereas estrogen-only preparations have been associated with more moderate increases in breast cancer risk in observational studies (15,16,18) and no (21) or a decreased risk (19,20,22) in randomized clinical trials. We showed that both estrogen-only and progestin-containing HT were associated with an increased risk of overall cancer and breast cancer in women oophorectomized at age 45 years or younger with a family history of cancer.

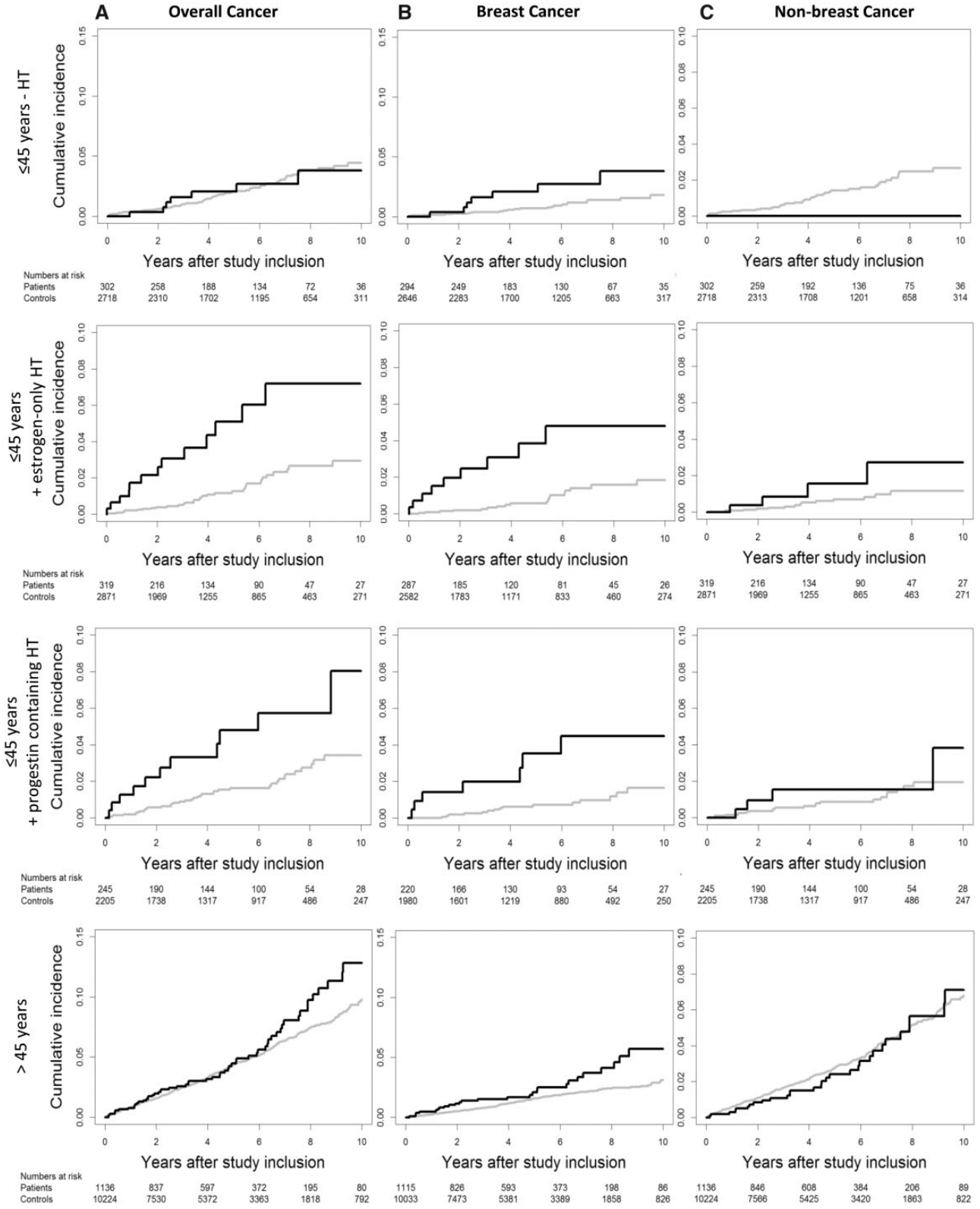

Figure 2. Cancer risk after bilateral prophylactic oophorectomy. Cumulative overall cancer **(A)**, breast cancer **(B)**, and nonbreast cancer **(C)** incidence after prophylactic oophorectomy in 302 women oophorectomized at age 45 years or younger – hormone therapy (HT; **black**), 2718 individuals from the population comparison cohort (**gray**), 319 women oophorectomized at age 45 years or younger + estrogen-only HT (**black**), 2871 individuals from the population comparison cohort (**gray**), 245 women oophorectomized at age 45 years or younger + progestin-containing HT (**black**), 2205 individuals from the population comparison cohort (**gray**), 1134 women oophorectomized at older than age 45 years (**black**), and 10 206 individuals from the population comparison cohort (**gray**). HT = hormone therapy.

Table 3. Cancer incidence rate ratios in women oophorectomized because of a family history of cancer who were unexposed to HT, exposed to two years or less of HT, and exposed to more than two years of HT compared with members of the population comparison cohort, Denmark, 1994–2016

	Overall cancer IRR (95% CI)	Breast cancer IRR (95% CI)
Cancer risk in time unexposed to HT*	1.17 (0.54 to 2.50)	2.83 (1.29 to 6.19)
Cancer risk in time exposed to ≤2 years of estrogen-only HT*	2.54 (1.12 to 5.82)	5.38 (2.12 to 13.61)
Cancer risk in time exposed to ≤2 years of progestin-containing HT*	3.10 (1.36 to 7.07)	3.94 (1.22 to 12.71)
Cancer risk in time exposed to >2 years of estrogen-only HT*	2.37 (1.15 to 4.89)	3.91 (1.53 to 9.96)
Cancer risk in time exposed to >2 years of progestin-containing HT*	1.25 (0.51 to 3.08)	2.70 (0.95 to 7.61)

*Vs population comparison controls. CI = confidence interval; HT = hormone therapy; IRR = incidence rate ratio.

With a registry-based study design, we were not able to control for menopausal status at the time of oophorectomy. Ninety-five percent of Caucasian women are premenopausal at the age of 45 years (35). Despite limited evidence (25–27), international guidelines (28) recommend systemic HT from the time of bilateral oophorectomy until the age of natural menopause. Thus, age 45 years was chosen as the cutoff point to make sure we studied the effects of HT on premenopausal women.

Our data showed that oophorectomized women more often had ER-negative breast cancers compared with the population comparison cohort. It is well known that BRCA-mutated women have a higher risk of ER-negative breast cancer (36), indicating a more aggressive nature of the cancers (30).

The effect of bilateral oophorectomy and subsequent use of HT on morbidity and mortality has been debated (8,11,12,37). We found that prophylactic oophorectomy at age 45 years or younger was associated with an increased risk of both low-energy fractures and infections. Use of HT did not influence these associations. We observed no increased risk of cardiovascular disease in oophorectomized women compared with the population comparison cohort irrespective of age at prophylactic oophorectomy. Other studies (38) have shown that cardiovascular risk is highly affected by time of the menopause and timing of hormone replacement.

Our study has some limitations. Data were obtained over a 22-year time period, and it cannot be excluded that changes in the composition of HT regimens over calendar time may impact effects on morbidity and mortality. The study relied on registry-based data, which may be inaccurate. However, data were extracted from the same data sources for both the oophorectomized women and the comparison cohort, minimizing the risk of differential misclassification, and thereby have minimal impact on estimates of relative risk. We cannot exclude that women taking HT after oophorectomy have characteristics that may confound our risk estimates of cancer. There was a limited number of deaths in women oophorectomized at age 45 years or younger, so mortality rates in this group should be interpreted with precaution.

We conclude that the use of HT in women oophorectomized at age 45 years or younger with a family history of cancer is associated with increased mortality and risk of overall cancer and breast cancer. Our study warrants further investigation to establish the impact of HT on mortality and cancer risk in oophorectomized women with a family history of cancer.

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