Research Article

Cancer Epidemiology, Biomarkers & Prevention

Postmenopausal Hormone Therapy and Breast Cancer Prognostic Characteristics: A Linkage between Nationwide Registries

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Abstract

Background: The effects of use of different types of hormone therapy on breast cancer risk according to prognostic factors are largely unknown.

Methods: We linked data from the Norwegian Prescription Database and the Cancer Registry of Norway during 2004 to 2009 on all women ages 45 to 79 years ($N = 686{,}614$). We estimated rate ratios and 95% confidence intervals for breast cancer in relation to hormone therapy using Poisson regression.

Results: During an average 4.8 years of follow-up, 7,910 invasive breast cancers were diagnosed. Compared with nonusers of hormone therapy, users of estradiol and tibolone were more likely to be diagnosed with grade I, lymph node–negative, and estrogen receptor–positive (ER^+)/progesterone receptor–positive (PR^+) tumors. However, compared with nonusers, users of the most common estrogen and progestin combinations [estradiol–norethisterone acetate (NETA) preparations (Kliogest, Activelle or Trisekvens)] were at a 4- to 5-fold elevated risk of grade I tumors, 3-fold elevated risk of lymph node–negative tumors, and 3- to 4-fold elevated risk of ER^+/PR^+ tumors. Importantly, estradiol–NETA users were also at a 2- to 3-fold increased risk of medium differentiated (grade II) tumors and tumors with lymph node involvement.

Conclusions: Use of oral estradiol, tibolone, and estradiol–NETA predominantly increases the risk of breast cancer with favorable prognosis characteristics. However, use of estradiol–NETA preparations also increases the risk of breast cancers with less favorable characteristics.

Impact: The hormone therapy preparations most commonly used in the Nordic countries are associated with both breast cancers with good and less favorable prognosis characteristics. *Cancer Epidemiol Biomarkers Prev; 25(11); 1464–73. ©2016 AACR.*

Introduction

There is convincing evidence that hormone therapy use is a risk factor for breast cancer (1–14). Use of combined estrogen–progestin therapy (EPT) has a substantially greater risk of breast cancer than preparations containing estrogen alone (ET; refs. 6, 7, 13–18), whereas the effect of tibolone has been less investigated (10, 19, 20).

A number of studies have reported an association between hormone therapy use and the occurrence of well-differentiated tumors with good prognostic characteristics (2, 21, 22), mostly estrogen receptor–positive (ER^+) and progesterone receptor–positive (PR^+) tumors (17, 23–25). Both ET and EPT have been associated with greater risks of invasive lobular cancer and tubular cancers than with invasive ductal cancer in a number of studies (21, 22, 26–33). However, there is limited evidence as to whether prognostic characteristics of tumors differ between users and nonusers of ET and EPT (17, 27, 32, 34–36). Until now, most studies have been limited by lack of statistical power or detailed information on hormone therapy types to allow for specific subgroup analyses.

We used information from the Norwegian population-based registries on redeemed prescriptions and cancer occurrence respectively, to investigate the effects of exposure to different components and preparations of hormone therapy on breast cancer risk according to hormone receptor status and other tumor characteristics.

Materials and Methods

Study population

The setting of this study has been described in detail elsewhere (18). Briefly, the study population consisted of all women born in Norway 1925–1959, alive and not emigrated as of January 1, 2004 (ages 45–79 years). This population was linked with the Norwegian Prescription Database (NorPD), which includes information on all redeemed prescriptions

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Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

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since 2004, and the incidence database at the Cancer Registry of Norway, which includes all cancer cases since 1953. Information on number of births, age at first birth, vital status, and emigration was obtained from the Norwegian population registry and Statistics Norway. Linkage between the registries was done using the unique personal identification number given to all Norwegian citizens at birth or immigration. The study was approved by the regional ethics committee in the South East region of Norway, and the Norwegian Data Protection Authority.

Among the 895,281 initially identified women, we excluded women born outside of Norway ($n = 94,333$), women with a cancer diagnosis before study start ($n = 52,074$), or a breast cancer diagnosis in the first 3 months of the study period (January–March 2004; $n = 531$). We also excluded women with prescriptions of sex hormones other than ET, tibolone, or EPT during the study period ($n = 33,299$) and women who only redeemed one prescription after July 1, 2004 ($n = 28,430$). This left 686,614 women for analyses. The women were followed for incident breast cancer and use of hormone therapy until December 31, 2008.

Identification of breast cancer cases

Cancer reporting is mandatory by law in Norway, and the Cancer Registry of Norway incidence database is 99% complete for solid tumors, including breast cancer (37). The registry records age at diagnosis, histologic grade, tumor size, lymph node involvement, and histologic subtype. Tumor size and lymph node involvement are classified according to the pTNM classification system and histologic grade is determined by the Nottingham criteria (38, 39). In the study period 2004–2008, information on ER and PR receptor status was available only for women who attended the national mammography screening program, which includes screen-detected and interval cancer cases diagnosed in women in the age range 50–69 years (plus 2-year follow-up for interval cancers). We used the cut-off points for ER and PR positivity defined by each laboratory, for most laboratories this was 10%. Among 7,910 incident invasive breast cancer cases in this study, ER status was available for 4,228 (53.5%) cases, and PR status was available for 4,208 (53.2%) cases.

Postmenopausal hormone use

Data on prescriptions redeemed for sex hormones [Anatomical Therapeutic Chemical (ATC) group G03] in the period 2004–2008 were retrieved from the Norwegian Prescription Database (www.norpd.no). Use of hormone therapy was defined as prescriptions for ET or EPT (ATC codes G03C and G03F, respectively). Hormone therapy in Norway includes the estrogen compounds estradiol and estriol, other estrogens (tibolone, with estrogenic, progestogenic, and weak androgenic activity), and combined regimens of estrogen–progestin containing estradiol and norethisterone acetate (NETA; Activelle, Kliogest, Trisekvens, Novofem). Use of progestin types other than NETA is almost nonexistent in Norway (40). Vaginal preparations of estradiol (Vagifem) and estriol (Ovesterin) are used for treatment of vaginal atrophy symptoms and contain lower amounts of estrogens compared with the oral formulations. Vaginal preparations are available without prescription in Norway, which means that the real use has been underestimated in our study.

All women redeeming a prescription for hormone therapy were considered as hormone therapy users. Duration of hormone therapy use was estimated for each hormone type as number of total treatment days, calculated from the package size, multiplied by the number of packages prescribed, and using the recommended dosing intervals. The women were included in the various type of hormone therapy preparation categories based on the specific product dispensed.

Follow-up

Person-years at risk for all women in the study population were calculated from start of the study period until censoring or end of follow-up. Women were censored at death, emigration, breast cancer diagnosis, other cancer diagnosis, or end of follow-up (December 31, 2008), whichever date occurred first. Women contributed person-years at risk as current users according to the accumulated duration of treatment for the type of hormone therapy dispensed. Nonusers contributed person-years at risk from January 1, 2004, until the date of the first redeemed prescription, if any, or end of the follow up. Breast cancer cases occurring during the first 3 months after start of use (current user) or after cessation of use (past user) were allocated to the former hormone therapy status category. These women contributed person-years to the former hormone therapy status from the estimated duration of use until the date of breast cancer diagnosis.

Hormone therapy use was categorized according to type of oral hormone therapy components and products and includes nonuser, past-user, estradiol, estriol, tibolone, Activelle, Kliogest, Trisekvens, and other types (which included users of vaginal and transdermal formulations, women who redeemed concurrent prescriptions of different components or preparations, and users of a number of other less representative hormone therapy preparations). Activelle, Kliogest, and Trisekvens are oral estradiol–NETA preparations of EPT. Activelle (1 mg estradiol and 0.5 mg NETA per day) and Kliogest (2 mg estradiol and 1 mg NETA per day) are continuous regimens. Trisekvens is a sequential EPT formulation with two tablet strengths of 2 or 4 mg estradiol for 22 days followed by 1 mg estradiol for 6 days, in addition to 1 mg NETA for 10 days in a 4 weeks cycle.

Statistical analysis

Incidence rate ratios (RR) with 95% confidence intervals (95% CI) of breast cancer associated with use of hormone therapy were estimated by Poisson regression. All regression models were adjusted for age in 5-year groups (45–49, 50–54, 55–59, 60–64, 65–69, 70–74, 75–79 years), number of births (nulliparous, 1, 2, 3, $\geq$4), age at first live birth (nulliparous, <25, 25–29, $\geq$30), and exposure time measured as person-years at risk (time offset in the Poisson regression model). We assessed whether risk differed by tumor characteristics: histologic grade (I, II, and III), tumor size ($\leq$1 cm, >1 and $\geq$2 cm, and > 2 cm), lymph node involvement (negative and positive), histology type (invasive ductal carcinoma and invasive lobular carcinoma), and for the subset with available data, ER status (negative and positive), PR status (negative and positive), and ER/PR status (ER^+ PR^+, ER^+ PR^-, and ER^- PR^-). Nonusers of hormone therapy were the reference group. All tests were two-sided with a 5% significance level. Statistical analyses were performed using SAS 9.2 (SAS Institute Inc.).

As hormone therapy users are more likely to undergo mammography, we assessed the effect of mammographic screening by calculating the risk estimates for hormone therapy use of the different components and formulations among screen and nonscreen detected cancers.

Results

The analysis database included 686,614 women that accumulated 3.3 million women-years, corresponding to an average follow-up of 4.8 years. A total of 178,383 women (26%) had redeemed hormone therapy prescriptions during the study period. The number of incident invasive breast cancer cases was 7,910.

The average duration of use of the formulations studied were 3.2 years for estradiol, 2.8 years for estriol, 2.7 years for tibolone, 2.6 years for Kliogest, 2.7 years for Activelle, and 2.3 years for Trisekvens. Oral estriol users were older at breast cancer diagnosis compared with nonusers, with 43.1% of estriol users 75 years or older, whereas users of Trisekvens were younger (Table 1). Compared with nonusers, the proportion of lobular tumors was

Table 1. Breast cancer characteristics by type of oral hormone therapy use assessed at the end of the follow-up period, 2004–2008 ($N = 7{,}910$)

	Hormone therapy use							
	Nonusers ($n = 5{,}602$)	**Estradiol users ($n = 143$)**	**Estriol users ($n = 120$)**	**Tibolone users ($n = 165$)**	**Kliogest users ($n = 272$)**	**Activelle users ($n = 555$)**	**Trisekvens users ($n = 93$)**	**Other users[a] ($n = 960$)**
Detection mode, *n* (%)								
Screen detected	2,208 (39.4)	63 (44.1)	31 (25.8)	81 (49.1)	134 (49.3)	301 (54.2)	41 (44.1)	419 (43.6)
Nonscreen detected	3,394 (60.6)	80 (55.9)	89 (74.2)	84 (50.9)	138 (50.7) $P < 0.05$[b]	254 (45.8) $P < 0.05$[b]	52 (55.9)	541 (56.4)
Age at diagnosis, mean (SD)	61.7 (9.8)	60.2 (6.5)	71.0 (7.9) $P < 0.05$[c]	60.3 (5.9)	62.4 (6.6)	61.0 (5.8)	55.0 (6.2) $P < 0.05$[c]	61.6 (7.9)
Histologic type, *n* (%)								
Ductal	4,506 (80.4)	110 (76.9)	94 (78.3)	131 (79.4)	202 (74.3)	426 (76.8)	73 (78.5)	753 (78.4)
Lobular	577 (10.3)	17 (11.9)	13 (10.8)	21 (12.7)	35 (12.9)	79 (14.2)	10 (10.8)	130 (13.5)
Tubular	90 (1.6)	3 (2.1)	1 (0.8)	4 (2.4)	10 (3.7)	20 (3.6)	4 (4.3)	21 (2.2)
Mucinous	122 (2.2)	4 (2.8)	4 (3.3)	4 (2.4)	3 (1.1)	10 (1.8)	1 (1.1)	17 (1.8)
Other	307 (5.5)	9 (6.3)	8 (6.7)	5 (3.0)	22 (8.1)	20 (3.6) $P < 0.05$[b]	5 (5.4)	39 (4.1)
Grading, *n* (%)								
I	1,085 (19.4)	36 (25.2)	17 (14.2)	45 (27.3)	79 (29.0)	185 (33.3)	26 (28.0)	237 (24.7)
II	2,474 (44.2)	65 (45.5)	66 (55.0)	77 (46.7)	120 (44.1)	248 (44.7)	39 (41.9)	413 (43.0)
III	1,309 (23.4)	26 (18.2)	17 (14.2)	31 (18.8)	30 (11.0)	81 (14.6)	20 (21.5)	184 (19.2)
Unknown	734 (13.1)	16 (11.2)	20 (16.7)	12 (7.3)	43 (15.8) $P < 0.05$[b]	41 (7.4) $P < 0.05$[b]	8 (8.6)	126 (13.1)
Tumor size, *n* (%)								
$\leq$1 cm	1,046 (18.7)	32 (22.4)	17 (14.2)	38 (23.0)	54 (19.9)	159 (28.6)	19 (20.4)	218 (22.7)
>1 cm and $\leq$2 cm	1,964 (35.1)	55 (38.5)	38 (31.7)	64 (38.8)	109 (40.1)	227 (40.9)	45 (48.4)	380 (39.6)
>2 cm	1,445 (25.8)	34 (23.8)	40 (33.3)	33 (20.0)	60 (22.1)	100 (18.0)	18 (19.4)	225 (23.4)
Unknown	1,147 (20.5)	22 (15.4)	25 (20.8)	30 (18.2)	49 (18.0)	69 (12.4) $P < 0.05$[b]	11 (11.8)	137 (14.3)
Lymph nodes, *n* (%)								
Negative	3,094 (55.2)	88 (61.5)	64 (53.3)	99 (60.0)	157 (57.7)	376 (67.7)	56 (60.2)	592 (61.7)
Positive	1,950 (34.8)	46 (32.2)	36 (30.0)	56 (33.9)	87 (32.0)	154 (27.7)	30 (32.3)	312 (32.5)
Unknown	558 (10.0)	9 (6.3)	20 (16.7)	10 (6.1)	28 (10.3)	25 (4.5) $P < 0.05$[b]	7 (7.5)	56 (5.8)
ER								
Negative	427 (7.6)	18 (12.6)	7 (5.8)	13 (7.9)	18 (6.6)	29 (5.2)	6 (6.5)	83 (8.6)
Positive	2,319 (41.4)	82 (57.3)	33 (27.5)	103 (62.4)	154 (56.6)	391 (70.5)	47 (50.5)	498 (51.9)
Unknown	2,856 (51.0)	43 (30.1)	80 (66.7)	49 (29.7)	100 (36.8)	135 (24.3) $P < 0.05$[b]	40 (43.0)	379 (39.5)
PR								
Negative	955 (17.0)	32 (22.4)	15 (12.5)	24 (14.5)	49 (18.0)	106 (19.1)	13 (14.0)	171 (17.8)
Positive	1,775 (31.7)	68 (47.6)	25 (20.8)	92 (55.8)	123 (45.2)	312 (56.2)	40 (43.0)	408 (42.5)
Unknown	2,872 (51.3)	43 (30.1)	80 (66.7)	49 (29.7) $P < 0.05$[b]	100 (36.8)	137 (24.7) $P < 0.05$[b]	40 (43.0)	381 (39.7)
ER PR								
ER^+ PR^+	1,722 (30.7)	64 (44.8)	23 (19.2)	90 (54.5)	119 (43.8)	306 (55.1)	37 (39.8)	393 (40.9)
ER^+ PR^-	581 (10.4)	18 (12.6)	10 (8.3)	13 (7.9)	35 (12.9)	83 (15.0)	10 (10.8)	103 (10.7)
ER^- PR^+	52 (0.9)	4 (2.8)	2 (1.7)	2 (1.2)	4 (1.5)	6 (1.1)	3 (3.2)	15 (1.6)
ER^- PR^-	374 (6.7)	14 (9.8)	5 (4.2)	11 (6.7)	14 (5.1)	23 (4.1)	3 (3.2)	68 (7.1)
Unknown	2,873 (51.3)	43 (30.1)	80 (66.7)	49 (29.7) $P < 0.05$[b]	100 (36.8)	137 (24.7) $P < 0.05$[b]	40 (43.0)	381 (39.7)

[a]Other includes vaginal/transdermal formulations, users of concurrent products, and users of other products not listed.
[b]Different at $P < 0.05$ in a two-sided test of equality for column proportions (z test) as compared with nonusers. The unknown category is excluded in the test for differences. Tests assume equal variances and are adjusted using the Bonferroni correction for multiple comparison.
[c]Different at $P < 0.05$ in a two-sided test of equality of means (t test) as compared with nonusers. Tests are adjusted using the Bonferroni correction for multiple comparison.

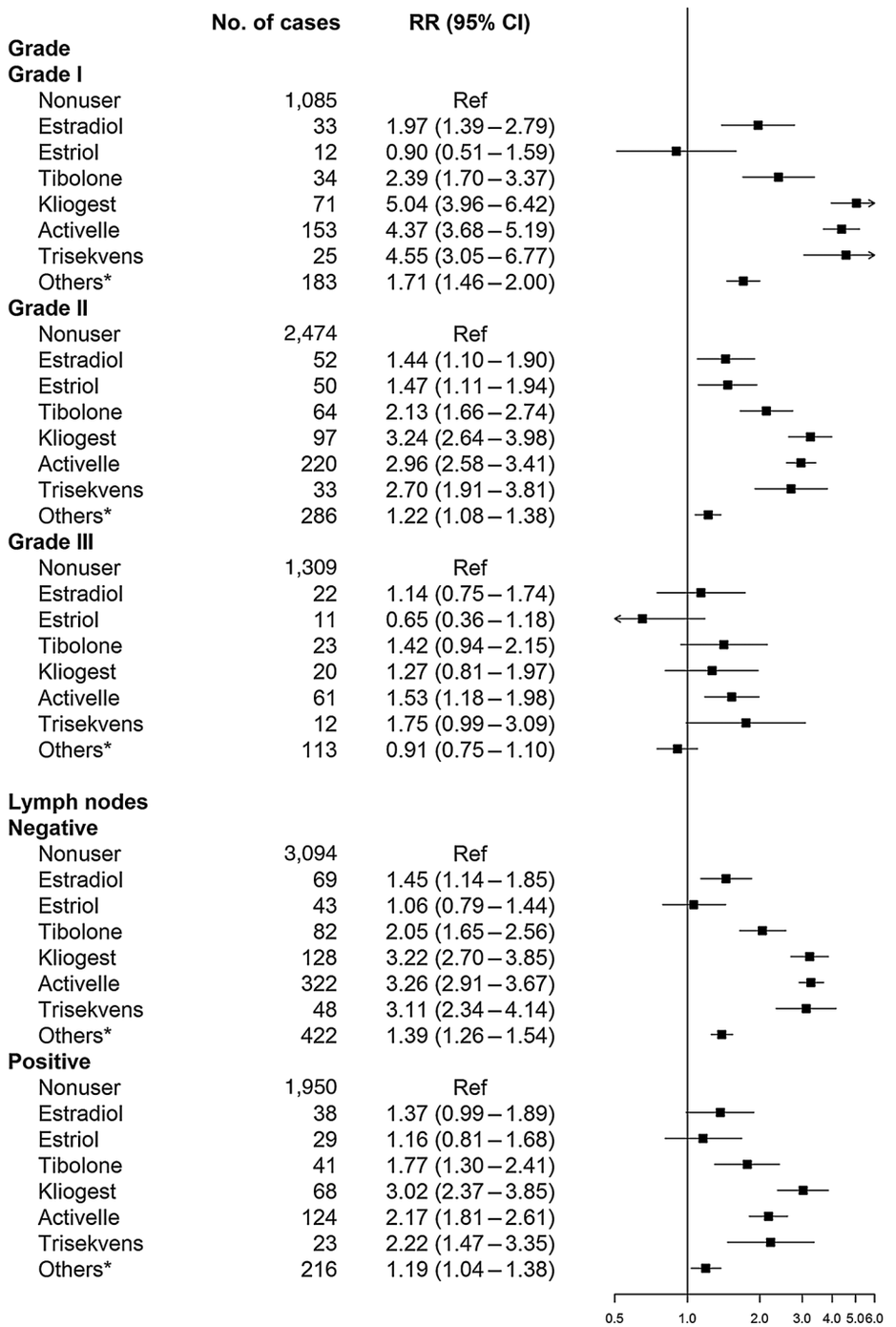

Figure 1.
Relative risk of invasive breast cancer by current use of different types of oral hormone therapy, histologic grade, and lymph node involvement. Adjusted for age (5-year), number of births, age at first birth and time (offset). *Others include vaginal/transdermal formulations, users of concurrent products, and users of other products not listed.

higher among users of Activelle, whereas users of Kliogest and Activelle had a higher proportion of histologic grade I tumors and a lower proportion of grade III tumors. Tumors smaller than 1 cm, lymph node negative tumors, and ER^+, PR^+, and ER^+/PR^+ tumors were more frequent among users of estradiol–NETA preparations of Activelle, whereas users of oral tibolone had a higher proportion of PR^+ and ER^+/PR^+ tumors.

Figures 1 and 2 show the associations between hormone therapy use and tumors with varying grade of differentiation, lymph node involvement, and tumor size. Considering nonusers of hormone therapy as the reference, use of oral estradiol, tibolone, Kliogest, Activelle, and Trisekvens was strongly associated with histologic grade I tumors, lymph node involvement negative tumors, and tumors sized $\leq$ 1 cm and 1 to 2 cm, but the association was weaker and less consistent with tumors with higher histologic grade, positive lymph node involvement (Fig. 1), and tumors >2 cm (Fig. 2). Use of the estradiol–NETA preparations Kliogest, Activelle,

	No. of cases	RR (95% CI)
Tumor size		
≤1 cm		
Nonuser	1,046	Ref
Estradiol	24	1.35 (0.90–2.03)
Estriol	12	1.03 (0.58–1.82)
Tibolone	31	2.04 (1.43–2.92)
Kliogest	44	2.97 (2.19–4.01)
Activelle	144	3.87 (3.24–4.62)
Trisekvens	17	3.08 (1.90–4.98)
Others*	160	1.45 (1.23–1.72)
>1 cm & ≤2 cm		
Nonuser	1,964	Ref
Estradiol	47	1.60 (1.20–2.14)
Estriol	27	1.08 (0.74–1.58)
Tibolone	55	2.22 (1.70–2.90)
Kliogest	87	3.58 (2.88–4.44)
Activelle	192	3.15 (2.71–3.66)
Trisekvens	37	3.65 (2.63–5.06)
Others*	258	1.36 (1.19–1.55)
>2 cm		
Nonuser	1,445	Ref
Estradiol	26	1.35 (0.91–1.99)
Estriol	30	1.38 (0.96–1.99)
Tibolone	24	1.53 (1.02–2.29)
Kliogest	48	3.03 (2.27–4.04)
Activelle	78	2.00 (1.58–2.51)
Trisekvens	13	1.86 (1.08–3.22)
Others*	161	1.26 (1.07–1.48)

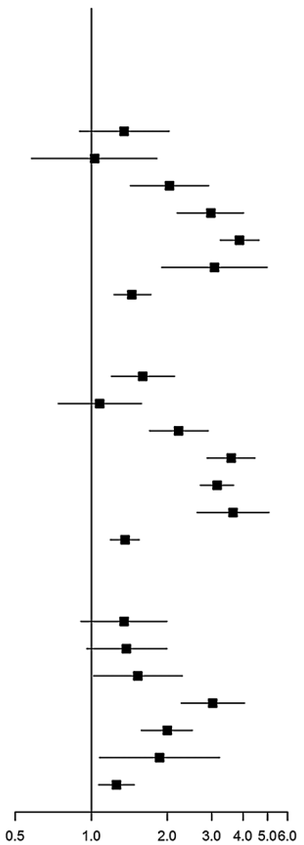

Figure 2.
Relative risk of invasive breast cancer by current use of different types of oral hormone therapy and tumor size. Adjusted for age (5-year), number of births, age at first birth and time (offset). *Others include vaginal/transdermal formulations, users of concurrent products, and users of other products not listed.

and Trisekvens was associated with a nearly 3-fold elevated risk of grade II tumors, and a 2- to 3-fold elevated risk of lymph node–positive tumors, as well as tumors >2 cm. For users of Kliogest there was no substantial difference in the risk estimates between the node positive or negative tumors, and between tumors of different sizes.

Use of oral formulations of estradiol was associated with a modestly increased risk of invasive ductal tumors and a 2-fold increased risk of lobular cancers (Fig. 3), whereas users of tibolone had an almost double risk of both ductal and lobular tumors. Use of estradiol–NETA preparations of Kliogest, Activelle, and Trisekvens was associated with a 2.5- to 3-fold increased risk of invasive ductal cancers and a 3.7- to 4.6-fold increased risk of invasive lobular tumors (Fig. 3).

Use of oral estradiol, tibolone, Kliogest, Activelle, and Trisekvens was more strongly associated with hormone receptor positive than receptor negative tumors (Fig. 4). However, use of Kliogest and Activelle was associated with a 2-fold elevated risk of PR^- tumors compared with nonusers, and use of the three estradiol–NETA preparations (Kliogest, Activelle, and Trisekvens) was associated with an increased risk of ER^+/PR^- tumors compared with nonusers.

The sensitivity analyses showed remarkably similar results as an overall, by histologic grade, by lymph node involvement, and by tumor size regardless of whether the cancer was detected at or outside of the national breast cancer screening program (Supplementary Tables S1–S4).

Discussion

In this large population-based cohort study, with exposure to hormone therapy based on a national registry on redeemed hormone therapy prescriptions in Norway, we found that, in general, use of the hormone therapy preparations studied was strongly associated with tumors with good prognostic characteristics (histologic grade I, no lymph node involvement, tumor size $\leq$ 2 cm, and hormone receptor–positive tumors) and invasive lobular cancers. However, we found that use of estradiol–NETA preparations (Kliogest, Activelle, and Trisekvens) was also associated with a 2- to 3-fold elevated risks of tumors with histologic grade II, lymph node involvement, and size >2 cm, and that Kliogest in particular was equally strongly associated with cancers with negative and positive lymph node involvement, and small and large size tumors.

Tumor characteristics

A number of studies have reported that hormone therapy use is predominantly associated with tumors with good prognosis characteristics (2, 22). A previous study found that hormone therapy use was more strongly associated with histologic grade I or II compared with grade III and also with a better prognosis score based on histologic grade, lymph node involvement, and tumor size (22). However, the increased risk of grade II, positive lymph node, and large size tumors found in our study with use of tibolone and estradiol–NETA is in agreement with a study that found an increased risk of tumors sized 2 to 5 cm among ET and

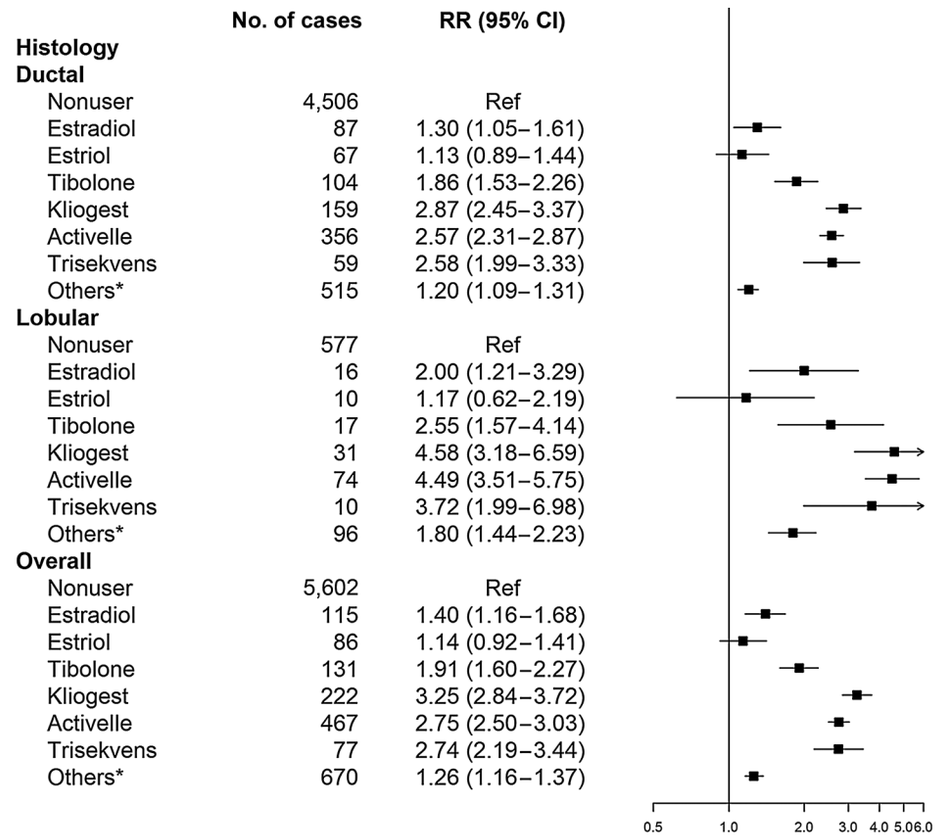

Figure 3.
Relative risk of invasive breast cancer by current use of different types of oral hormone therapy and histology type. Adjusted for age (5-year), number of births, age at first birth and time (offset). *Others include vaginal/transdermal formulations, users of concurrent products, and users of other products not listed.

EPT users (17). This finding supports the hypothesis that specific ET and EPT components carry an increased risk of breast cancer not limited to localized good prognosis tumors.

Histologic subtype

We found that use of oral estradiol, tibolone, and estradiol–NETA preparations (Kliogest, Activelle, and Trisekvens) were associated with both invasive ductal and invasive lobular carcinomas, with a stronger association for invasive lobular compared with invasive ductal cancers. Our results of an increased risk for invasive ductal carcinoma with current use of ET and EPT has previously been reported (26, 29, 31, 32, 36, 41–44), although other published studies showed no association (21, 27, 28, 34, 35). A greater risk of lobular cancer or mixed ductal–lobular cancer compared with ductal cancer are in agreement with most published studies (21, 23, 26–28, 30–32, 34–36, 43, 44), but not with others (15). Invasive lobular cancers have been associated with a better short- and long-term survival and a better stage-matched prognosis than women with invasive ductal cancer (45, 46), although the data are not completely consistent (47).

Hormone receptors of breast cancers

Previous studies have shown a stronger association of hormone therapy use with hormone receptor–positive breast tumors (2, 17, 23, 24, 29). Consistently, we found that use of estradiol, tibolone, and estradiol–NETA preparations of Kliogest, Activelle, and Trisekvens was most strongly associated with ER^+ and PR^+ tumors. The risk was also elevated for ER^+/PR^- tumors whereas no association was found for ER^-/PR^- tumors. This is consistent with other studies (17, 23), although lack of statistical power has to be considered for ER^-/PR^- tumors. There were too few ER^-PR^+ tumors (1.1% of all breast malignancies), to provide any reliable estimates for this subgroup.

Tibolone

To our knowledge, this is the first study to analyze the association of tibolone with tumor characteristics. Tibolone is a tissue-specific regulator claimed to be less risky for the breast than natural estrogen therapies (48, 49). However, we found tibolone to be more strongly associated with the various tumor subgroups studied than natural estrogen components of estradiol. Previous studies have shown an increased breast cancer risk in tibolone users compared with ET users (10, 19). Similarly to EPT users, we found that use of tibolone was associated with an overrepresentation of tumor subgroups conferring a favorable prognosis, but also with an elevated risk of more advanced breast cancers with less beneficial characteristics, although the intensity of the associations was of a lesser magnitude.

Estradiol–NETA preparations

Several studies have suggested that the higher risks found in European compared with U.S. studies might be partially explained by the greater use of estradiol–NETA in Europe as opposed to the more common medroxyprogesterone in the United States (50). However, few studies have been able to directly compare these medications, as most populations use

	No. of cases	RR (95% CI)
Estrogen receptor		
ER+		
Nonuser	2,319	Ref
Estradiol	66	1.51 (1.18–1.93)
Estriol	23	1.08 (0.72–1.63)
Tibolone	81	2.08 (1.66–2.59)
Kliogest	132	3.58 (3.00–4.27)
Activelle	329	3.46 (3.08–3.89)
Trisekvens	43	3.34 (2.47–4.52)
Others*	360	1.34 (1.20–1.50)
ER−		
Nonuser	427	Ref
Estradiol	14	1.66 (0.98–2.83)
Estriol	8	2.13 (1.05–4.30)
Tibolone	9	1.17 (0.60–2.26)
Kliogest	12	1.72 (0.97–3.05)
Activelle	17	0.91 (0.56–1.48)
Trisekvens	3	1.20 (0.39–3.75)
Others*	46	0.89 (0.65–1.20)
Progestogen receptor		
PR+		
Nonuser	1,775	Ref
Estradiol	58	1.75 (1.34–2.27)
Estriol	21	1.30 (0.85–2.01)
Tibolone	75	2.53 (2.00–3.19)
Kliogest	106	3.79 (3.11–4.61)
Activelle	270	3.73 (3.28–4.25)
Trisekvens	37	3.72 (2.68–5.15)
Others*	300	1.47 (1.30–1.66)
PR−		
Nonuser	955	Ref
Estradiol	22	1.19 (0.78–1.81)
Estriol	10	1.13 (0.60–2.11)
Tibolone	15	0.90 (0.54–1.50)
Kliogest	38	2.43 (1.75–3.36)
Activelle	74	1.82 (1.43–2.31)
Trisekvens	9	1.70 (0.88–3.28)
Others*	104	0.92 (0.75–1.12)
ER/PR Receptor		
ER+ PR+		
Nonuser	1,772	Ref
Estradiol	55	1.71 (1.31–2.24)
Estriol	19	1.21 (0.77–1.91)
Tibolone	74	2.57 (2.04–3.25)
Kliogest	103	3.80 (3.12–4.64)
Activelle	265	3.79 (3.32–4.31)
Trisekvens	35	3.63 (2.59–5.08)
Others*	291	1.47 (1.30–1.67)
ER+ PR−		
Nonuser	581	Ref
Estradiol	11	0.98 (0.54–1.79)
Estriol	4	0.72 (0.27–1.93)
Tibolone	7	0.70 (0.33–1.48)
Kliogest	29	3.03 (2.08–4.40)
Activelle	62	2.54 (1.95–3.31)
Trisekvens	8	2.58 (1.28–5.19)
Others*	67	0.99 (0.76–1.27)
ER− PR−		
Nonuser	374	Ref
Estradiol	11	1.50 (0.82–2.73)
Estriol	6	1.82 (0.81–4.09)
Tibolone	8	1.19 (0.59–2.39)
Kliogest	9	1.48 (0.76–2.87)
Activelle	12	0.74 (0.41–1.31)
Trisekvens	1	0.46 (0.06–3.25)
Others*	37	0.81 (0.58–1.14)

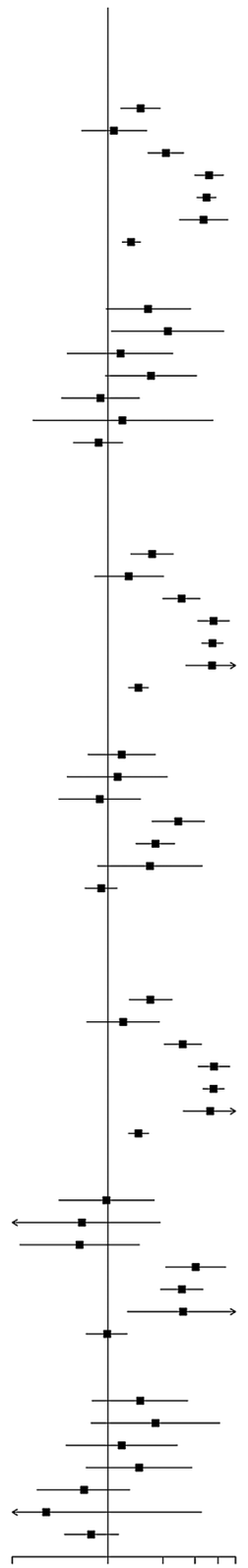

Figure 4.
Relative risk of invasive breast cancer by current use of different types of oral hormone therapy and hormone receptor status. Adjusted for age (5-year), number of births, age at first birth and time (offset). *Others include vaginal/transdermal formulations, users of concurrent products, and users of other products not listed.

either one or the other. Those that have attempted have not yielded consistent results (10, 36, 51). We found a strong and consistently increased risk associated with use of estradiol–NETA preparations. The lower dose preparation Activelle (1 mg estradiol and 0.5 mg NETA daily) conferred similarly increased risks for good prognosis characteristics to the highest NETA dose preparation Kliogest (2 mg estradiol and 1 mg NETA daily). However, we found a significantly higher risk for lymph node positive and large tumors in users of Kliogest compared with Activelle. The high risk of poor prognosis characteristics associated with the high-dose preparation Kliogest is of particular concern. Prescribing the lowest biologically effective dose of progestin might be expected to minimize the risk of breast cancer. Although Kliogest was withdrawn from the Norwegian market in 2010, it is still available elsewhere. Activelle is currently being used in Norway and in a number of other countries. It should be noted that our statistical power to test some of the differences between formulations was limited and should be considered carefully.

Breast cancer detection by mammography

Women who go to regular screening mammography are more likely to be diagnosed with an early-stage cancer, but may also be more likely to use hormone therapy (52). We did not have individual-level information on screening history of women in the study population, but we had information on whether breast cancers were detected at mammography screening or outside the screening program. Interestingly, the sensitivity analyses comparing screen and nonscreen detected cancers showed remarkably similar results regardless of whether the cancer was detected within or outside the screening program.

Strengths and limitations

A major strength of this study is that the data on hormone therapy exposure and breast cancer occurrence was obtained from linkage of nationwide population-based registries. All redeemed prescriptions of hormone therapy and all detected breast cancers in Norwegian women ages 45 to 79 years by 2004 are included. The information on components, preparations, and duration of use of each preparation adds to the strength, as opposed to self-reported hormone therapy use. The Cancer Registry was established in 1952, which means that we were able to exclude all women with earlier or prevalent cancer by 2004. The study included nearly 700,000 women, which provided sufficient statistical power to analyze various tumor subgroups and hormone therapy exposures.

However, the study has several limitations. First, we had no information on hormone therapy use before study start. A number of current users may have been users prior to 2004, so total durations of use may be higher and the risk could be overestimated. However, a number of our presumed never users may have used hormones prior to the study start, which could underestimate the risk. Our study was also limited by the number of women with missing information for some subtype analyses. In particular, ER and PR status were not widely collected for all cases during the study period (available for 53% of breast cancer cases). We also lacked information on possible confounding factors such as age at menopause, income, body mass index, physical activity, or family history of breast cancer. Norwegian data from the 1980s showed that hormone therapy users had higher education and income, were leaner, but differed minimally by physical activity compared with nonusers (53). Nonetheless, we think that neither factor is a strong enough risk factor to have accounted for the observed effects.

Conclusion

Our study suggests that current hormone therapy users of oral estradiol, tibolone, and estradiol–NETA preparations had an increased risk of good prognosis tumors. However, users of estradiol–NETA preparations were at a 2- to 3-fold elevated risk of grade II tumors, breast cancers with lymph node involvement, and tumors >2 cm. Thus, the hormone therapy preparations most commonly used in the Nordic countries were associated with breast cancers with both good and less good prognostic characteristics.

Disclosure of Potential Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): M. Román, S. Graff-Iversen, E. Weiderpass, S. Vangen, S. Hofvind, G. Ursin

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