Menopausal Hormone Therapy and Risk of Clinical Breast Cancer Subtypes

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Abstract

Background: **Breast cancer is a heterogeneous disease with subtypes that may vary in their etiologies. Menopausal hormone therapy has been associated more strongly with lobular and tubular than ductal histologic types and with tumors that are smaller, hormone receptor–positive, and of lower grade. At the same time, correlations have been observed between histology and clinical characteristics. To identify those tumor subtypes most strongly associated with hormone therapy use, it is necessary to disentangle these interrelationships.**

Methods: **Based on 3,464 postmenopausal breast cancer cases and 6,657 controls from the population-based Mammary carcinoma Risk factor Investigation study, we used polytomous logistic regression to evaluate associations between hormone therapy use and risk of invasive breast cancer subtypes. We assessed variations in risk for selected tumor characteristics among histologic and hormone receptor subtypes, both overall and for specific hormone therapy regimens.**

Results: **Lobular and mixed types showed less variation by prognostic factors than did ductal tumors. Current hormone therapy use had the strongest associations with prognostic variables in estrogen receptor (ER)-positive and/or progesterone receptor (PR)-positive ductal tumors and in lobular tumors regardless of ER/PR status, with little effect on ER/PR-negative ductal tumors. The observed associations varied minimally by hormone therapy type or regimen.**

Conclusion: **Current hormone therapy use was associated with more favorable breast cancer characteristics for ductal tumors but had less effect on prognostic characteristics in women with lobular tumors. Both histologic type and estrogen receptor/progesterone receptor status seem to be important in explaining the role of hormone therapy in the etiology of breast cancer subtypes.** (Cancer Epidemiol Biomarkers Prev 2009;18(4):1188–96)

Introduction

Breast cancer is a heterogeneous disease, and research suggests that subtypes may vary in their etiologies (1). Menopausal hormone therapy, particularly combined estrogen-progestagen therapy, has been shown to increase breast cancer risk and has been implicated in the increased incidence of breast cancer observed over the past three decades (2-4). A number of studies in recent years have looked at the influence of hormone therapy on breast cancer tumor pathology and most of them have concluded that tumors arising under hormone therapy have a more favorable prognostic profile. Hormone therapy has been found to confer greater risk on invasive lobular, tubular, and mixed ductal-lobular histologic types (5-7)—types associated with better outcomes in some but not all studies—than for invasive ductal cancers. In addition, hormone therapy–associated tumors have been shown to be smaller (8-11), hormone receptor positive (12-14), of lower grade (14-18), and to have fewer affected nodes (9, 19) than tumors not associated with hormone therapy use. However, due to the strong correlation between histologic type and clinical characteristics, in particular estrogen receptor/progesterone receptor (ER/PR) status (20-24), it is unclear which tumor subtypes are most strongly associated with hormone therapy use. To date, only three published studies have attempted to disentangle these interrelationships (22, 25, 26), and only one stratified their findings beyond histologic type (22). Using data from a large German population–based case-control study, we aim to estimate the risk of invasive breast cancer subtypes associated with current hormone therapy use, with particular emphasis on categories of ER/PR status within histologic subgroups.

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Materials and Methods

Study Population: Cases and Controls. The current report is based on data from the Mammary carcinoma Risk factor Investigation (MARIE) study, the details of which have been described elsewhere (5). Briefly, women were eligible for inclusion if they were between age 50

and 74 y, German-speaking, living in either the Hamburg or the Rhein-Neckar-Karlsruhe region, and had a histologically confirmed primary invasive or *in situ* breast cancer [International Classification of Diseases 10 pos. C50 (malignant neoplasm of breast)] and D05 (carcinoma *in situ* of breast) diagnosed between either January 1st, 2001, and September 30th, 2005, (Hamburg region), or between August 1st, 2002, and July 31st, 2005, (Rhein-Neckar-Karlsruhe region). The study was approved by the ethics committees of both the University of Heidelberg and the Medical Association of Hamburg and conducted in accordance with the Declaration of Helsinki. All study participants gave written informed consent. Cases were identified through hospital admissions, surgery schedules and pathology records, and through the Hamburg cancer registry. Two controls per case were randomly selected from population registries and frequency matched by birth year and study region to the cases. A standardized questionnaire was used during face-to-face interviews to obtain information on several known and suspected breast cancer risk factors. Comprehensive data were collected on use of menopausal hormone therapy, including timing and duration, type and brand name of hormone therapy, dose, method of administration, as well as reasons for initiating and terminating therapy.

Pathology. Clinical and pathologic tumor characteristics were abstracted from hospital records and pathology reports. Pathohistologic testing was conducted in accordance with the Level 3 guidelines for breast cancer early detection for Germany, based on the European guidelines for quality assurance in mammography screening (27). Tumors were categorized histologically as ductal, lobular, mixed ductal-lobular (mixed), and, for purposes of this analysis, all others. In the case of multiple phenotype components of a tumor, the predominant proportion was given priority in the diagnosis. Grading of all invasive carcinomas was based on a modification of Bloom and Richardson, recommended by Elston and Ellis (28). Size and nodal status data were extracted from tumor-node-metastasis status. Hormone receptor status was ascertained using immunohistochemical testing, with immunoreactive scoring according to Remmele and Stegner (29). Her2/neu overexpression was assessed using standardized immunohistochemical testing, followed up, in the case of a weak positive reaction, by a fluorescent in situ hybridization test.

Variable Definitions. Never use of hormone therapy was defined as a total of ≤3 mo of use. Current use of hormone therapy was defined as a total of >3 mo of use within the last 6 mo before the reference date. Women were defined as postmenopausal if they reported their last natural menstrual bleeding at least 12 mo before the reference date, or a bilateral oophorectomy, or cessation of menses due to treatment of diseases other than breast cancer by either radiation or chemotherapy. Those above age 55 y whose menopausal status was unclear because of hysterectomy or hormone use were also considered postmenopausal (because the 90th percentile for age at menopause for women with natural menopause was 55 y) but assigned an unknown age at menopause. Both premenopausal women and women under age 55 y, whose menopausal status was unclear because of hysterectomy or hormone therapy, were excluded from this analysis. Despite being a known confounder of hormone therapy and breast cancer risk, age at menopause was not included in the final models because age at menopause could not be determined for women with a hormone therapy–associated menopause or with hysterectomy (see Flesch-Janys and colleagues 2008 for a comprehensive description of the authors' approach to menopausal status and age).

Population for Analysis. Of the 3,464 cases of the study, a total of 3,245 invasive breast tumors were histologically confirmed. Of these, complete corresponding hormone therapy data were available for 3,234. Further data on tumor grade were available for 3,228 (99.8%), size for 3,133 (96.9%), nodal status for 3,044 (94.1%), ER/PR status for 3,197 (98.9%), and Her2/neu overexpression for 2,919 (90.3%). The control group consisted of 6,657 women.

Statistical Analysis. Adjusted odds ratios (OR) and 95% confidence intervals (95% CI) were calculated using polytomous logistic regression (SPSS 12; procedure NOMREG) and adjusted for study center and year of birth (≤1934, 1935-1939, 1940-1944, 1945-1949, ≥1950). For purposes of this analysis, invasive histologic types were categorized into ductal, lobular/tubular, and mixed ductal-lobular (mixed). In the case of models further stratified by ER/PR status, small cell size made it necessary for us to combine the last two categories into a single category of lobular/tubular/mixed. All other histologic categories were excluded from the risk analysis, as their small numbers and widely varying clinical characteristics precluded separate analyses or combining categories (n = 95).

Separate models used a different combination of tumor characteristics as the outcome variable. The basic model was composed of three histologic types (ductal, lobular/tubular, and mixed) further cross-classified with either two (in the case of ER/PR status and Her2/neu overexpression) or three (in the case of grade, size, and affected nodes) gradations plus the category ''0'' representing the controls. The independent variables included hormone therapy status [never (reference), past, current] and type of current hormone therapy [monoestrogen, cyclical estrogen-progestagen, continuous estrogen-progestagen versus never hormone therapy (reference)]. The advanced models differed from the basic in that they were composed of a combination of two histologic groups (ductal and lobular/tubular/mixed) plus hormone receptor status (ER+ and/or PR+, and ER− and PR−), cross-classified with the aforementioned gradations of tumor characteristics. Covariates in the fully adjusted models originated from a list of potential breast cancer risk factors and factors correlated with hormone therapy use [year of birth (continuous), study center, age at menarche, parity, ever breastfed, ever benign breast tumor, number of mammograms, family history of breast cancer, occupation, type of menopause, and body mass index]. Differences between effect estimates of hormone therapy use on gradations of tumor characteristics were tested via a χ^2 test for heterogeneity, taking into account the covariance of the effect estimates.

Table 1. Distribution of tumor characteristics and menopausal hormone therapy use by major invasive histologic type

	Ductal n = 2,224*	Lobular/tubular n = 765	Mixed ductal-lobular n = 151
	n (%)	n (%)	n (%)
Grade†			
1	388 (17.4)	178 (23.3)	24 (15.9)
2	1,070 (48.1)	501 (65.5)	95 (62.9)
3+	759 (34.1)	81 (10.6)	32 (21.2)
Unknown	7 (0.3)	5 (0.7)	0 (0.0)
Size‡			
TI	1,250 (56.2)	429 (56.1)	84 (55.6)
T2	775 (34.8)	251 (32.8)	57 (37.7)
T3+	122 (5.5)	64 (8.4)	6 (4.0)
Unknown§	77 (3.5)	21 (2.7)	4 (2.6)
Nodes			
0	1,368 (61.5)	489 (63.9)	94 (62.3)
1	524 (23.6)	155 (20.3)	37 (24.5)
2+	203 (9.1)	70 (9.2)	13 (8.6)
Unknown§	129 (5.8)	51 (6.7)	7 (4.6)
ER/PR status			
ER+ and/or PR+	1,718 (77.2)	712 (93.1)	138 (91.4)
ER− and PR−	481 (21.6)	38 (5.0)	9 (6.0)
Unknown	25 (1.1)	15 (2.0)	4 (2.6)
Her2/neu			
Negative	1,536 (69.1)	609 (79.6)	111 (73.5)
Positive	461 (20.7)	85 (11.1)	27 (17.9)
Unknown	227 (10.2)	71 (9.3)	13 (8.6)
Use of hormone therapy‖			
Never	804 (36.1)	174 (22.7)	44 (28.8)
Ever	1,420 (63.7)	591 (77.0)	107 (69.9)
Current¶	944 (42.4)	437 (56.9)	83 (54.2)
Unknown	5 (0.2)	3 (0.4)	2 (1.3)

*n, number among that histologic type for which data on hormone therapy status were available.
†1, well-differentiated (low grade); 2, moderately differentiated (intermediate grade); 3+, poorly differentiated or undifferentiated (high grade).
‡T1, ≤2 cm; T2, >2 to ≤5 cm; T3+, >5 cm.
§High proportion of missing values due to lack of preoperative data on size and nodal status for cases exposed to neoadjuvant chemotherapy.
‖Includes cases with unknown hormone therapy status, thus making the total number higher than that given in each column head. In addition, the total number of cases with complete hormone therapy data does not total 3,234, due to the exclusion of all other histological types.
¶For controls, current use of hormone therapy was n = 2205.

Results

Characteristics of Tumors by Histologic Type. Of all invasive tumors, 68.7% were ductal, 23.7% lobular/tubular, 4.7% mixed ductal-lobular, and 2.9% other. Ductal tumors were proportionately more likely than lobular/tubular and mixed tumors to be grade III+ and less likely to be grade II. Ductal tumors were also proportionately more likely to be ER− and PR−, and to be Her2/neu positive. Neither the distribution of tumor size nor the number of affected nodes varied substantially by histologic type (Table 1).

Overall, for the three main histologic types, 46.5% of cases were current users of hormone therapy, compared with 33.4% of controls. Menopausal hormone therapy use was differentially distributed by histologic type, with lobular/tubular and mixed types both more likely than ductal types to include ever and current users of hormone therapy (ever, 77.0% and 69.9% versus 63.7%; current, 56.9% and 54.2% versus 42.4%, respectively).

Hormone Therapy–Associated Tumors: Prognostic Factors by Histologic Type. Compared with never users of menopausal hormone therapy, current users of hormone therapy were more likely to present with small than midsize tumors, both among ductal [T1: OR, 1.74 (95% CI, 1.50-2.03); T2: OR, 1.18 (95% CI: 0.98-1.41)] and among lobular/tubular [T1: OR, 3.74 (95% CI, 2.84-4.92); T2: OR, 2.36 (95% CI, 1.72-3.24)] histologic types (Table 2). In addition, hormone therapy–associated tumors had fewer affected nodes than did nonhormone therapy–associated tumors, both among ductal [N0: OR, 1.60 (95% CI, 1.39-1.85); N2+: OR, 0.69 (95% CI, 0.48-0.99)] and among mixed types [N0: OR, 3.82 (95% CI, 2.20-6.63); N1: OR, 1.24 (95% CI, 0.60-2.55)]. No other tumor characteristic showed statistically significantly differential risks for hormone therapy–associated cancer across more than one histologic type. Hormone therapy–associated ductal tumors were more likely to be grade 1 than grades 2 or 3+ [G1: OR, 2.60 (95% CI, 2.00-3.39); G2: OR, 1.41 (95% CI, 1.20-1.65); G3+: OR, 0.99 (95% CI, 0.82-1.19)], and more likely to be hormone receptor positive than negative [ER+ and/or PR+: OR, 1.49 (95% CI, 1.31-1.69); ER− and PR−: OR, 1.02 (95% CI, 0.81-1.29)]. Elevated risks for hormone therapy–associated lobular/tubular tumors were independent of ER/PR status but were higher for Her2/neu negative than positive tumors [Her2/neu negative: OR, 3.24 (95% CI, 2.59-4.06); Her2/neu positive: OR, 1.72 (95% CI, 1.04-2.86)].

Tests for heterogeneity between histologic types showed that the greatest differences were between ductal and lobular/tubular types; all gradations of tumor characteristics, with the exception of grade 1 and Her2/neu

positive, were highly statistically significant. We observed no significant differences between lobular/tubular and mixed types, for any category of tumor characteristic.

Hormone Therapy–Associated Tumors: Tumor Characteristics by Histologic ER/PR Subtypes. Further stratification of our main models by hormone receptor status (Fig. 1) revealed differential risks by tumor characteristics for histologic subtypes according to ER/PR status. We observed that among ER+ and/or PR+ ductal tumors, the risk estimates for grade, size, nodal status, and Her2/neu were almost identical to those observed in the nonstratified models. However, among ER− and PR− ductal tumors, there was no evidence of either an increased overall risk or differential risk by clinical characteristics. Among the ER+ and/or PR+ lobular/tubular/mixed tumors, we observed an increased overall risk and a weak positive trend toward better prognostic factors, again similar to those observed in the main models. In contrast to the ductal group, the increased risk for receptor-positive lobular/tubular/mixed tumors was observed at nearly the same order of magnitude among the ER− and PR− tumors, albeit based on very few cases.

Tests for heterogeneity comparing the two ER− and PR− strata revealed statistically significant differences for grade 2 (*p(het)* 0.03), nodes 0 (*p(het)* 0.01), and Her2/neu negative (*p(het)* 0.02), in addition to tumor size subtypes T2 (*p(het)* 0.001) and T3 (*p(het)* <0.0001) (data not shown).

Hormone Therapy–Associated Tumors: Hormone Therapy Type and Regimen. Additional stratification of the above findings by type and regimen of hormone therapy did not reveal evidence of differential risk (Table 3). Reflecting the pattern for overall breast cancer risk observed in our previous analysis (5), risk estimates for the majority of tumor characteristic gradients increased steadily from monoestrogen through cyclical estrogen-progestagen up to continuous estrogen-progestagen therapy. Any deviation from expected risk estimates may be due to small subgroup size, particularly among lobular/tubular/mixed ER− and PR− tumors (data not shown).

Discussion

It is important to first acknowledge the limitations of this study. Histopathologic data were collected from a number of participating pathologists, rather than from a single, centralized source. However, the distribution of gradations of tumor characteristic by histologic type was similar to that seen in a large study in which pathology was centrally assessed by a single pathologist (22). The second weakness involved our limited statistical power

Table 2. ORs for specific tumor subtypes, by major invasive histologic type, among current versus never users of hormone therapy

	Ductal		Lobular/tubular		Mixed ductal-lobular		*P* (ductal vs lob/tub)	*P* (ductal vs mixed)	*P* (mixed vs lob/tub)
	*n/n**	OR† (95% CI)	*n/n*	OR (95% CI)	*n/n*	OR (95% CI)			
Grade									
1	221/93	2.60 (2.00-3.39)	108/36	3.22 (2.15-4.82)	17/4	5.62 (1.76-17.97)	0.38	0.21	0.37
2	461/391	1.41 (1.20-1.65)	288/109	3.29 (2.58-4.20)	52/27	2.34 (1.42-3.85)	<0.0001	0.05	0.22
3+	258/319	0.99 (0.82-1.19)	39/26	2.02 (1.18-3.44)	14/13	1.52 (0.67-3.45)	0.01	0.31	0.57
P‡ (G1 vs G2)		<0.0001		0.93		0.17			
P (G1 vs G3+)		<0.0001		0.17		0.07			
Size									
TI	603/365	1.74 (1.50-2.03)	265/78	3.74 (2.84-4.92)	53/19	3.26 (1.87-5.66)	<0.0001	0.03	0.66
T2	293/329	1.18 (0.98-1.41)	134/68	2.36 (1.72-3.24)	28/19	1.86 (0.99-3.47)	<0.001	0.17	0.50
T3+	26/74	0.52 (0.32-0.84)	28/21	2.46 (1.31-4.59)	2/2	2.38 (0.29-19.30)	<0.001	0.17	0.42
P (T1 vs T2)		<0.01		0.03		0.19			
P (T1 vs T3+)		<0.0001		0.23		0.78			
Nodes									
0	632/434	1.60 (1.39-1.85)	296/98	3.54 (2.75-4.55)	60/19	3.82 (2.20-6.63)	<0.0001	<0.01	0.80
1	209/209	1.28 (1.03-1.58)	85/39	2.51 (1.67-3.77)	17/15	1.24 (0.60-2.55)	<0.01	0.93	0.09
2+	54/106	0.69 (0.48-0.99)	32/22	2.06 (1.15-3.70)	4/6	1.38 (0.35-5.43)	<0.01	0.34	0.60
P (N0 vs N1)		0.07		0.15		0.01			
P (N0 vs N2+)		<0.0001		0.09		0.18			
ER/PR status									
ER+ and/or PR+	768/611	1.49 (1.31-1.69)	407/164	2.97 (2.42-3.64)	77/39	2.46 (1.62-3.73)	<0.0001	0.02	0.42
ER− and PR−	160/188	1.02 (0.81-1.29)	21/8	3.48 (1.47-8.28)	2/5	0.62 (0.11-3.62)	0.01	0.59	0.09
P		<0.01		0.72		0.14			
Her2/neu									
Negative	661/544	1.42 (1.24-1.63)	352/129	3.24 (2.59-4.06)	66/28	2.83 (1.77-4.55)	<0.0001	0.01	0.61
Positive	176/188	1.10 (0.88-1.39)	42/30	1.72 (1.04-2.86)	9/12	1.07 (0.42-2.73)	0.11	0.95	0.38
P		0.05		0.02		0.07			

Abbreviations: Lob, lobular; tub, tubular.

*n, the number of current hormone therapy users/never hormone therapy users. Sum of n differs from Table 1 because past hormone therapy users not included.

†ORs adjusted for year of birth (continuous), study center, ever breastfed, ever benign breast tumor, number of mammograms, and family history of breast cancer.

‡All *P*s represent tests for heterogeneity.

with respect to some gradations of tumor characteristics, particularly after stratification by ER/PR status and hormone therapy type and regimen. Finally, we used a binary variable to represent ER/PR status (ER− and PR− versus ER+ and/or PR+), precluding a more nuanced analysis of hormone receptor status.

In this analysis, we found that breast cancer tumors associated with current hormone therapy use vary in their prognostic characteristics by histologic type, with stronger effects on ductal subtypes than on lobular/tubular and mixed histologic types. Furthermore, we found that this difference could not be explained by ER/PR status, as we observed differential risks by tumor characteristics for histologic subtypes according to ER/PR status. Finally, type and regimen of current hormone therapy use did not affect the patterns of the observed associations.

We were unable to identify any studies in the literature examining differences in prognostic variables for hormone therapy–associated tumors in which results were simultaneously stratified by both histologic type and ER/PR status. Previous studies have presented data on hormone therapy–associated tumor characteristics either by histologic type (25, 26), by ER status (30), or by hormone therapy regimen (15, 17, 31-33). An additional study simultaneously adjusted for several prognostic factors in a single model, including histologic type, grade, size, and nodal status, with ER/PR status as a potential confounder (22). However, the authors reported their findings as the single prognostic factor most strongly associated with hormone therapy use, thus not allowing for a direct comparison with our stratified results.

Consistent with the literature reporting that hormone therapy use is associated with a stronger overall increase in the risk of lobular/tubular/mixed than ductal tumors, we observed that current hormone therapy use increased the risk of each lobular/tubular and mixed subtype, with few exceptions. Although we found current hormone therapy use to be associated with increased risk for nearly all gradations of tumor characteristics among lobular/tubular and mixed tumors, it was only among ductal types that we observed consistent and, with two exceptions, statistically significant decreases in the risk of poorer gradations of grade, size, nodal status, ER/PR status, and Her2/neu overexpression. Li and colleagues (26) also observed that among lobular and mixed ductal-lobular tumors, each gradation of tumor stage, size, or nodal status was significantly associated with current hormone therapy use, but that among ductal tumors, significantly increased risks were only seen for the lowest stage, smallest size, and negative nodal status. Despite the overrepresentation of higher grade tumors among ductal types shown in our descriptive data, we found that ductal types under current hormone therapy use were far more likely to be of the lowest grade. The reasons for this are not entirely clear. It is not likely to be explained by surveillance bias because, in contrast to size and nodal status, grade does not change as a tumor progresses (34). We were unable to locate any other published study that included tumor grade in its presentation of tumor characteristics by histologic type in hormone therapy users; thus, we could not compare our findings on this factor. A study that used a novel statistical model allowing for simultaneous adjustment for grade, size, nodal status, and histologic type found grade to be significantly associated with recent or current use of combined estrogen-progestagen therapy. However, the association with grade was independent of histologic type (22).

Although it is encouraging from a public health perspective that ductal tumors, linked in many studies with more aggressive phenotypes and poorer overall survival, seem in current hormone therapy users to be associated with significantly better prognostic factors, it is not clear if this, in turn, leads to lower recurrence and improved survival among current hormone therapy users. Indeed, the Women's Health Initiative study, a randomized controlled trial, observed a higher risk of advanced disease, in the form of larger tumors and more nodal invasion, among current combined estrogen-progestagen therapy users (35). A systematic review by

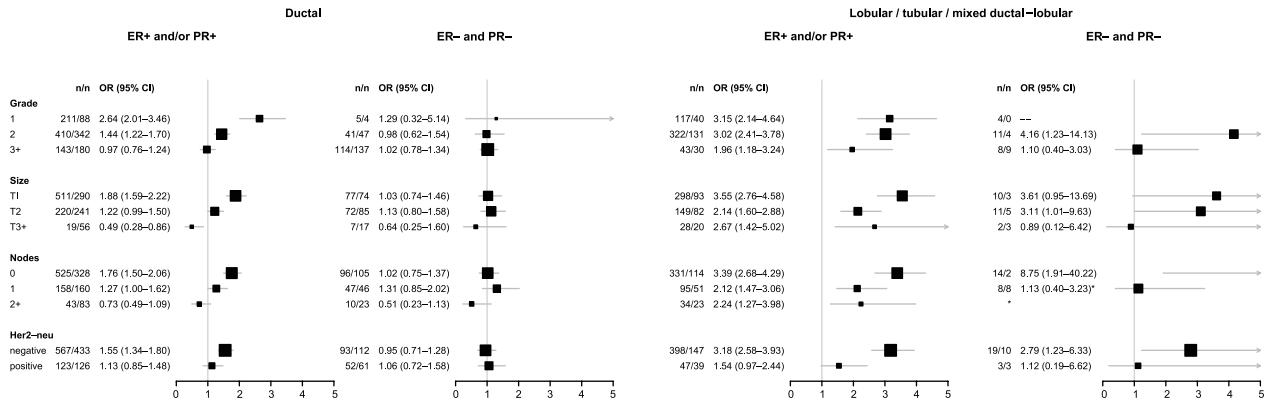

Figure 1. ORs for the risk of gradations of tumor characteristics, stratified by ER/PR status and major invasive histological type, among current versus never users of hormone therapy. ORs derived by polytomous logistic regression for different histological and ER/PR subtypes are shown with 95% CIs. The reference group is comprised of never users of hormone therapy. N depicts the number of current hormone therapy users/never hormone therapy users (with the corresponding numbers for controls being 2205/2685). The size of the box is proportional to the number of included cases. All models adjusted for year of birth, study center, family history of breast cancer, ever benign breast disease, ever breastfed and number of mammograms; *, categories for nodes 1, 2, and 3 combined.

Table 3. ORs for specific tumor subtypes, stratified by major invasive histologic type, ER/PR status, and hormone therapy type/regimen, among current versus never users of hormone therapy

A.

	Ductal: ER+ and/or PR+					
	Monoestrogen		Cyclical estrogen-progestagen*		Continuous estrogen-progestagen	
	n/n[†]	OR[‡] (95% CI)	*n/n*	OR (95% CI)	*n/n*	OR (95% CI)
Grade						
1	39/88	2.10 (1.41-3.14)	33/88	2.17 (1.41-3.34)	111/88	3.60 (2.65-4.90)
2	61/342	0.87 (0.65-1.17)	80/342	1.47 (1.12-1.93)	198/342	1.80 (1.47-2.20)
3+	26/180	0.73 (0.47-1.12)	34/180	1.23 (0.84-1.82)	59/180	1.03 (0.75-1.42)
Size						
TI	81/290	1.25 (0.96-1.64)	99/290	1.94 (1.50-2.51)	243/290	2.32 (1.90-2.83)
T2	40/241	0.90 (0.63-1.28)	36/241	1.02 (0.70-1.49)	117/241	1.67 (0.30-2.13)
T3+	4/56	0.41 (0.15-1.16)	7/56	0.93 (0.41-2.10)	4/56	0.26 (0.09-0.74)
Nodes						
0	81/328	1.14 (0.87-1.48)	100/328	1.79 (1.39-2.32)	258/328	2.25 (1.86-2.72)
1+	40/243	0.89 (0.62-1.27)	35/243	0.98 (0.67-1.43)	97/243	1.34 (1.04-1.74)
Her2/neu						
Negative	100/433	1.12 (0.88-1.43)	110/433	1.55 (1.22-1.98)	269/433	1.91 (1.60-2.29)
Positive	15/126	0.59 (0.34-1.02)	28/126	1.33 (0.90-2.14)	60/126	1.38 (0.99-1.94)

B.

	Ductal: ER− and PR−					
	Monoestrogen		Cyclical estrogen-progestagen		Continuous estrogen-progestagen	
	n/n	OR (95% CI)	*n/n*	OR (95% CI)	*n/n*	OR (95% CI)
Grade						
1	0/4	—	3/4	4.38 (0.92-20.88)	2/4	1.38 (0.24-8.02)
2	9/47	0.80 (0.37-1.73)	8/47	1.05 (0.49-2.27)	17/47	1.06 (0.59-1.92)
3+	26/137	0.97 (0.63-1.50)	16/137	0.76 (0.45-1.30)	53/137	1.24 (0.88-1.75)
Size						
TI	18/74	0.99 (0.57-1.71)	11/74	0.82 (0.43-1.56)	34/74	1.22 (0.79-1.88)
T2	11/85	0.70 (0.37-1.33)	15/85	1.21 (0.69-2.14)	35/85	1.39 (0.91-2.12)
T3+	3/17	1.11 (0.31-3.94)	1/17	0.48 (0.06-3.69)	2/17	0.48 (0.11-2.15)
Nodes						
0	24/105	1.07 (0.67-1.69)	17/105	0.97 (0.57-1.66)	43/105	1.16 (0.79-1.71)
1+	7/69	0.47 (0.20-1.08)	10/69	0.95 (0.48-1.89)	26/69	1.27 (0.79-2.05)
Her2/neu						
Negative	17/112	0.71 (0.42-1.23)	21/112	1.13 (0.70-1.85)	40/112	1.04 (0.70-1.53)
Positive	14/61	1.13 (0.62-2.07)	3/61	0.33 (0.10-1.05)	26/61	1.44 (0.88-2.34)

C.

	Lobular/tubular/mixed ductal-lobular: ER+ and/or PR+					
	Monoestrogen		Cyclical estrogen-progestagen		Continuous estrogen-progestagen	
	n/n	OR (95% CI)	*n/n*	OR (95% CI)	*n/n*	OR (95% CI)
Grade						
1	20/40	2.19 (1.25-3.84)	25/40	3.68 (2.17-6.24)	54/40	3.88 (2.50-6.01)
2	54/131	1.93 (1.37-2.72)	55/131	2.83 (2.00-3.99)	164/131	4.18 (3.23-5.41)
3+	7/30	1.30 (0.56-3.03)	11/30	2.64 (1.28-5.44)	15/30	1.72 (0.90-3.31)
Size						
TI	47/93	2.22 (1.52-3.22)	52/93	3.39 (2.35-4.91)	151/93	4.88 (3.67-6.49)
T2	28/82	1.53 (0.97-2.41)	34/82	2.64 (1.72-4.04)	66/82	2.50 (1.76-3.55)
T3+	5/20	1.92 (0.69-5.30)	5/20	2.68 (0.96-7.44)	13/20	3.38 (1.59-7.17)
Nodes						
0	57/114	2.32 (1.64-3.26)	61/114	3.43 (2.44-4.83)	165/114	4.57 (3.49-5.97)
1+	21/74	1.32 (0.79-2.21)	25/74	2.22 (1.38-3.58)	58/74	2.53 (1.75-3.66)
Her2/neu						
Negative	68/147	2.10 (1.54-2.87)	77/147	3.32 (2.45-4.52)	191/147	4.12 (3.23-5.24)
Positive	7/39	0.95 (0.42-2.17)	5/39	0.87 (0.34-2.26)	27/39	2.32 (1.37-3.94)

NOTE: All three tables shown include parts of the same statistical model for respective tumor characteristics (grade, size, nodes). Although also part of these models, lobular/tubular/mixed ER− and PR− subtype data are not presented here, due to very small numbers after stratification by hormone therapy type and regimen.

*Estrogen-progestagen: combined estrogen-progestagen menopausal hormone therapy.

† *n*, current hormone therapy users/never hormone therapy users (with corresponding numbers for controls being monoestrogen, 546/2,685; cyclical estrogen-progestagen, 422/2,685; and continuous estrogen-progestagen, 853/2,685).

‡ ORs adjusted for same potential confounders as in Table 2.

Antoine and colleagues (36) on hormone therapy use and breast cancer morbidity and mortality showed, in fact, that most published data contradict these findings, although the authors argue that this might be due to the influence of publication bias or biases associated with retrospective study designs. Since that review, two prospective cohort studies comprising ~15,000 women have been published, and both observed better survival among current hormone therapy users, with associations persisting even after adjustment for screening, stage, and other confounders (17, 37).

Lobular/tubular and mixed tumors are more likely than ductal types to be ER/PR positive. A number of studies have found an association between hormone therapy use and likelihood of positive ER/PR status (12-14), although null findings have also been observed (11, 38). Hormone therapy–associated tumors are more often lobular/tubular or mixed than ductal. Some studies (39-41) but not others (42, 43) have found invasive lobular tumors to be associated with better survival than invasive ductal tumors. Based on this information, we hypothesized that associations between hormone therapy use and histologic type could potentially be attributed to ER/PR status, and that an analysis of tumor characteristics considering categories of ER/PR status separately by histologic type would reveal that better prognostic profiles are limited to ER+ and/or PR+ tumors. In fact, we observed differential risks by clinical characteristics for histologic types based on ER/PR status: Among lobular/tubular/mixed types, the prognostic profiles for ER+ and/or PR+ and ER− and PR− types were nearly identical in the magnitude of their risk estimates, whereas among ductal tumors the increased likelihood of favorable prognosis was limited to ER+ and/or PR+ types. However, caution should be taken not to overinterpret the results of our lobular/tubular/mixed ER− and PR− findings, as very small numbers did not allow for stable risk estimates. To our knowledge, ours is the first study to describe such a differential association between hormone therapy use and ER/PR status by histologic type. A recent report on mortality associated with different categories of ER/PR status by histologic type found that ER− and PR− tumors had increased mortality across nearly all histologic types (ductal and lobular types were categorized together), irrespective of their tumor characteristics (44). How this might relate to our findings is not clear, in particular because the authors did not include hormone therapy in their analysis. A biological or mechanistic explanation for our finding that current hormone therapy use could be associated with a good prognostic profile for lobular/tubular/mixed ER− and PR− tumors but not for ductal ER− and PR− tumors is lacking. Further studies will be needed to corroborate these findings.

We observed that smaller tumor size and fewer affected nodes characterized hormone therapy–associated tumors among all three histologic subtypes, to varying degrees. Better surveillance among hormone therapy users might explain these findings, in which case hormone therapy use could be considered a proxy for health care access or health behavior. Daling and colleagues (25) also observed smaller and lower stage ductal tumors among hormone therapy users, but the association disappeared after adjustment for screening. However, the screening variable used in our models was associated with a ≤10% change in the risk estimate for tumor size, and adjustment for screening in the nodal status model did not diminish the observed associations, thus minimizing the likelihood of such bias in our study. Nonetheless, because the possibility of residual confounding remains, we are unable to entirely exclude the effect of better surveillance among hormone therapy users as an explanation.

Another possible explanation for smaller tumors and less nodal spread is that in estrogen-progestagen therapy, progesterone may exert an inhibitory effect on already existent breast malignancies, depending on regimen of hormone therapy use, whereby singular pulses of progesterone may induce, whereas subsequent pulses may arrest growth (45). However, we did not observe effect modification of our findings by hormone therapy type and regimen, although we did see minor inconsistencies in our patterns of risk estimates for combination estrogen-progestagen therapy. The small numbers in these subcategories do not allow for further interpretation.

In summary, although the overall magnitude of risk associated with current use of hormone therapy was greater among lobular/tubular and mixed ductal-lobular histologic types, ductal tumors seemed to have a more favorable prognostic profile under current hormone therapy use. Stratification by ER/PR status suggested that only among ductal histologic types did the prognostic profiles differ by ER/PR subtype: The increased likelihood of favorable prognosis was limited to ER+ and/or PR+ tumors, whereas ER− and PR− tumors showed no evidence of either an increased overall risk or differential risk by clinical characteristics. We observed no significant differential risk for hormone therapy type or regimen. Both histologic type and ER/PR status seem to be important in explaining the role of menopausal hormone therapy in the etiology of breast cancer subtypes.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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