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RESEARCH

Breast Tumor Characteristics in Hormone Replacement Therapy Users

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Abstract The aim of this study was to further elucidate the influence of HRT use, regarding duration, regimen and route of administration, on breast tumor characteristics. We evaluated the associations between HRT use and breast tumor characteristics in 530 postmenopausal women diagnosed with invasive breast cancer. Detailed information on HRT use and mammographic attendance were collected through a postal questionnaire. Adjusted odds ratios and 95% confidence intervals were calculated using logistic regression. Tumors in HRT users were significantly smaller, more often of ductal histologic type and with lower grade and lower mitotic index compared to tumors in nonusers. Tumor characteristics did not vary significantly by HRT duration, regimen and route of administration, except for mitotic index, which was more often of score 2 in long-term users, and of score 3 in short-term users. Higher mammographic surveillance among HRT users did not explain our results. We conclude that tumors in HRT users have a more favorable prognostic profile regardless of duration, regimen and route of administration. These effects seem to be due to the influence of HRT on preexisting tumors causing their greater differentiation rather than earlier detection due to mammographic surveillance.

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Introduction

Hormone replacement therapy (HRT) use is associated with increased risk of breast cancer [1]. A modest increase in risk is seen with long-term use (more than 5 years) and appears to be greater for current users of combined estrogen and progestin HRT [2, 3].

The only randomized controlled trial, the Women's Health Initiative (WHI) study, comparing estrogen plus progestin HRT with placebo reported women in the treated arm to had slightly larger tumors that were more likely to be lymph node positive and were diagnosed at a more advanced stage [4]. In contrast, a number of observational studies that have searched for the influence of HRT use on breast tumor pathology have concluded that tumors arising under HRT have a more favorable prognostic profile, i.e. postmenopausal HRT has been associated more strongly with lobular and tubular tumors, histological types that correspond to better outcomes than ducal tumors [5, 6]. HRT-associated tumors have also been shown to be smaller, hormone receptor (HR) positive, better differentiated (lower grade) and to have fewer affected lymph nodes than tumors not arising under HRT [7–17]. In addition, several studies indicated a favorable survival after breast cancer among HRT users compared with nonusers. The improved survival rates were mainly confined to current users [17, 18].

It remains unclear if tumor characteristics differ between users and nonusers in relation to HRT duration, regimen and route of administration. Furthermore, there is still insufficient evidence whether favourable tumor character-

istics are due to biological effects of HRT. It has been argued that these associations could be attributed to higher mammographic surveillance in HRT users, which might lead to earlier diagnosis and thereby to favorable tumor characteristics and survival [4].

To further elucidate the influence of HRT use on breast tumor characteristics in terms of duration, regimen and route of administration, we conducted a retrospective case series of 530 postmenopausal women diagnosed with invasive breast cancer holding information on mammographic examinations before the diagnosis as a possible confounding factor.

Patients and Methods

Study Population

The study is an extension of a case-control study performed in Slovenia from 2006 to 2008. For the purposes of the present study we used information from cases only. Briefly, postmenopausal women diagnosed with invasive primary breast cancer between January 1, 2006 and December 31, 2008 at the Institute of Oncology Ljubljana, who were 50–69 years old at the time of diagnosis, and of Caucasian ethnic origin were eligible for inclusion in the study. The women were invited to participate via a personal letter and asked to complete an enclosed written questionnaire. The overall response rate was 82.5% (825/1000) for breast cancer cases. A lower response rate among controls led us to randomly exclude further 295 cases. Thus, the analyses reported herein are based on the remaining case series of 530 breast cancer cases. They were subdivided according to the HRT status into two groups; 157 HRT users and 373 nonusers.

Informed written consent was obtained from all women enrolled in the study. The study protocol was approved by the National Medical Ethics Committee of the Republic of Slovenia.

Data Collection

In addition to general information (socioeconomic status, weight, height), data on reproductive factors (age at menarche, number of pregnancies, age at first delivery, number of deliveries, breastfeeding, age at menopause), attending a mammography examination, family history of breast and/or ovarian cancer (first-degree relatives), smoking and alcohol consumption were collected by means of a postal questionnaire. Detailed questions were asked regarding drug intake, sex hormones in particular (oral contraceptive—OC use, HRT use). A color chart displaying all preparations ever marketed in Slovenia was included in the questionnaire to aid recall. Women were identified as postmenopausal if they had achieved either natural or surgical menopause. Information was obtained on HRT duration (3 categories; nonusers: never or less than 1 year, short-term users: 1<5 years, long-term users: 5 or more years), regimen (estrogen therapy, estrogen plus progestin therapy), and route of administration (systemic (and local), local only). HRT use for less than 1 year was considered no use. Recent mammography was defined as mammography within 2 years (yes, no) in order to cover the normal 2-year interval of mammographic screening program.

We retrieved information on tumor characteristics from the pathology reports in the patient's medical records. Tumor grading was performed according to the Nottingham scheme [19]. HR status (estrogen receptor—ER, progesterone receptor—PR) was assessed by immunohistochemistry (IHC), using monoclonal rabbit ER antibody, Clone SP1 (Neomarkers, Fremont, CA, USA) and monoclonal mouse anti-human PR antibody, Clone PgR 636 (DAKO corp., CA, USA). Tumors were categorized as ER or PR positive if nuclear staining was observed in at least 10% of nuclei. Human epidermal growth factor receptor 2 (HER2) status was determined by both, IHC (HercepTest^{TM}, DAKO corp., CA, USA) and dual-color FISH (PathVysion® HER2 DNA probe kit and Paraffin pretreatment kit, both Abbot-Vysis, Inc., Downers Grove, IL, USA). HER2 was considered positive when scored 3+ on the IHC and/or the ratio of HER2 signal to chromosome 17 signal in 60 cells by FISH analysis scored >2.2.

Statistical Analyses

We used the independent t-test to compare the values of the means between HRT users and nonusers; continuous variables are presented as means±standard deviation (SD). Distributions of categorical tumor characteristics in relation to HRT use, duration of HRT use, HRT regimen and route of HRT administration were assessed using chi-square test; categorical variables are presented as counts and percentages. Odds ratios (ORs) and the corresponding 95% confidence intervals (CI) were calculated using logistic regression analysis. In the first analysis, adjustment for age at diagnosis as a continuous variable, years of OC use (never or <1, 1<5, 5<10, 10 or more) and any first-degree relative with breast and/or ovarian cancer (yes, no) was performed. In the subsequent analysis, adjustment by age at diagnosis as a continuous variable, years of OC use (never or <1, 1<5, 5<10, 10 or more), any first-degree relative with breast and/or ovarian cancer (yes, no) and recent mammography (yes, no) was performed. P-value <0.05 was considered statistically significant. All statistical analyses were done using SPSS 18.0 software package (SPSS, Chicago, IL, USA).

Results

Distribution of HRT Use, Recent Mammography Examinations and Breast Tumor Characteristics Among Study Subjects (Tables 1 and 2)

The study population consisted of 530 postmenopausal women aged 50–69 years (mean±SD, 60.45±5.84 years) diagnosed with invasive breast cancer. Approximately one third of the patients (n=157, 29.6%) were using HRT prior to diagnosis, 14.3% for short-term (less than 5 years) and 15.3% for long-term (5 years or more). Among HRT users, more than two thirds (n=131, 71.2%) were using combined estrogen plus progestin HRT.

The vast majority of patients (n=444, 84.9%) had invasive ductal carcinoma, followed by invasive lobular carcinoma (n=62, 11.9%) and other special types of carcinoma (n=17, 3.2%) of which there were mucinous, tubular, cribriform and medullary carcinomas. Distributions of other patient and tumor characteristics are presented in Tables 1 and 2.

Distributions of Patient and Breast Tumor Characteristics in Relation to HRT Use (Table 3)

The mean ages for HRT users and nonusers were 60.70± 5.04 and 60.34±6.15 years, respectively, and did not differ significantly between the groups (p=0.517). As expected, older patient age significantly correlated with HR-positive breast cancers (p=0.046) with the odds of developing a HR-positive tumor increasing by 4.2% per year (OR 1.042, 95% CI 1.001–1.085). On the contrary, the likelihood of developing HER2-positive breast cancer decreased by 4.9% per year (OR 0.951, 95% CI 0.908–0.996) (p=0.035).

Smaller tumor size, lower grade and lower mitotic index were more often found among HRT users compared with nonusers. Additionally, HRT users attended a recent mammography more often (87.1% vs. 56.6%). No statistically significant difference among HRT users and nonusers was noted in the distribution of histologic type of the tumor, tubular formation, nuclear atypia, lymphovascular invasion, lymph node status, HR status and HER2 status.

Distributions of Breast Tumor Characteristics Among HRT Users in Relation to Duration of HRT Use (Table 4), HRT Regimen and Route of HRT Administration

Tumor characteristics did not vary significantly by duration of HRT use, except for mitotic index, which was more often of score 2 in long-term users, and of score 3 in short-term users. Neither did tumor characteristics vary significantly by HRT regimen and route of HRT administration (data not shown).

Associations of HRT Use and Breast Tumor Characteristics (Table 5)

Additionally, we performed logistic regression analyses to evaluate the associations between HRT use and breast tumor characteristics adjusting for age at diagnosis, years of OC use and any first-degree relative with breast and/or ovarian cancer. Only significant associations are summarized in Table 5. HRT users were half less likely to be diagnosed with lobular than with ductal cancer (OR 0.5, 95% CI 0.3-1.1). HRT use was also associated with smaller

Table 1 Distribution of HRT use and recent mammography examinations among study subjects

Patient characteristics		Study subjects n=530	Study subjects %
Mean age (± SD) (years)		60.45±5.84	
HRT use	Nonusers: 0<1 years	373	70.4
	Short-term users: 1<5 years	76	14.3
	Long-term users: ≥5 years	81	15.3
	Missing data	0	
Regimen of HRT[a]	Estrogen only	53	28.8
	Estrogen plus progestin	131	71.2
	Missing data	2	
Route of HRT administration[a]	Local only	39	21.2
	Systemic (and local)	145	78.8
	Missing data	2	
Recent mammography	No	180	34.4
	Yes	344	65.6
	Missing data	6	

[a] Among those who ever used HRT.

Table 2 Distribution of breast tumor characteristics among study subjects

Tumor characteristics		Study subjects n=530	Study subjects %
Histologic type	Ductal	444	84.9
	Lobular	62	11.9
	Special-type	17	3.2
	Missing data	7	
Tumor size	≤ 20 mm	349	67.2
	21–50 mm	152	29.3
	> 50 mm	18	3.5
	Missing data	11	
Histopathologic grade	1	89	17.1
	2	227	43.6
	3	205	39.3
	Missing data	9	
Tubular formation	1	33	6.3
	2	143	27.5
	3	344	66.2
	Missing data	10	
Nuclear atypia	1	16	3.1
	2	267	51.3
	3	237	45.6
	Missing data	10	
Mitotic index	1	219	42.3
	2	141	27.2
	3	158	30.5
	Missing data	12	
Lymphovascular invasion	No	403	79.3
	Yes	105	20.7
	Missing data	22	
Lymph node involvement	No	288	57.5
	Yes	213	42.5
	Missing data	29	
HR status	ER-PR-	83	15.7
	ER+and/or PR+	444	84.3
	Missing data	3	
HER2 status	HER2-	449	87.7
	HER2+	63	12.3
	Missing data	18	

tumor sizes, the risk of having tumor size >50 mm was OR 0.1 (95% CI 0.02-0.9) for HRT users compared with nonusers. Furthermore, the OR of being diagnosed with a grade 3 tumor rather than of a grade 1 tumor was 0.5 (95% CI 0.3-0.8) for HRT users compared with nonusers. Similarly, HRT users were half less likely to have a mitotic index of score 2 (OR 0.6, 95% CI 0.4-0.9) or score 3 (OR 0.5, 95% CI 0.3-0.9) than score 1.

As we found higher mammographic surveillance in HRT users, which might lead to earlier diagnosis of breast cancer, and thereby to favorable histological features, we repeated the regression analysis but this time adjusting for age at diagnosis, years of OC use, any first-degree relative with breast and/or ovarian cancer and recent mammography. The ORs were only marginally influenced by recent mammography attendance, the results thus being almost the same as those where recent mammography was not included in the final regression model.

Discussion

This study has demonstrated favorable prognostic features in the breast tumors of patients receiving HRT prior

Table 3 Distribution of patient and breast tumor characteristics in relation to HRT use

Patient and tumor characteristics		HRT use, n (%)		p-value
		0<1 year *n*=373	≥1 years *n*=157	
Mean (±SD) age (years)		60.70±5.04	60.34±6.15	0.517
Histologic type	Ductal	304 (82.6)	140 (90.3)	0.079
	Lobular	50 (13.6)	12 (7.8)	
	Special-type	14 (3.8)	3 (1.9)	
Tumor size	≤ 20 mm	**236 (64.6)**	**113 (73.4)**	0.029
	21–50 mm	**112 (30.7)**	**40 (26.0)**	
	> 50 mm	**17 (4.7)**	**1 (0.6)**	
Histological grade	1	**56 (15.3)**	**33 (21.2)**	0.039
	2	**153 (42.0)**	**74 (47.4)**	
	3	**156 (42.7)**	**49 (31.4)**	
Tubular formation	1	23 (6.3)	10 (6.5)	0.076
	2	90 (24.7)	53 (34.2)	
	3	252 (69.0)	92 (59.3)	
Nuclear atypia	1	12 (3.3)	4 (2.6)	0.195
	2	178 (48.8)	89 (57.4)	
	3	175 (47.9)	62 (40.0)	
Mitotic index	1	**138 (37.9)**	**81 (52.6)**	0.008
	2	**106 (29.1)**	**35 (22.7)**	
	3	**120 (33.0)**	**38 (24.7)**	
Lymphovascular invasion	No	281 (78.9)	122 (80.3)	0.735
	Yes	75 (21.1)	30 (19.7)	
Lymph node involvement	No	200 (56.8)	88 (59.1)	0.643
	Yes	152 (43.2)	61 (40.9)	
HR status	ER-PR-	61 (16.5)	22 (14.0)	0.476
	ER+and/or PR+	309 (83.5)	135 (86.0)	
HER2 status	HER2-	311 (86.4)	138 (90.8)	0.166
	HER2+	49 (13.6)	14 (9.2)	
Recent mammography	No	**160 (43.4)**	**20 (12.9)**	<0.001
	Yes	**209 (56.6)**	**135 (87.1)**	

Statistically significant results are shown **in bold**.

to diagnosis. Tumors in HRT users were significantly smaller, more often of ductal histologic type and with lower grade and lower mitotic index compared to tumors in nonusers.

In contrast to existing literature, we found no difference between HRT users and nonusers in the distribution of lymphovascular invasion and lymph node involvement. Furthermore, HR status and HER2 status did also not differ considerably between the groups. The evidence suggests that the relationship between HRT use and consequent development of HR-positive breast cancer is stronger and observed sooner or only in current users of combined estrogen and progestin HRT [11, 12, 20–22]. Unfortunately, we did not collect data to differentiate prior from current users. Still, there was a trend towards an increase in HR-positive disease among HRT users, especially among long-term users, users of combined and of systemic hormone preparations. However, larger studies are required for these effects to be significant. Reports on the association between HRT use and HER2 status are still sparse. In order to confirm the findings of the better outcomes seen in tumors arising in women taking HRT, the HRT use should not prove to be related to HER2 overexpression. In concordance, a case-control study by Biglia et al. described no difference in HER2 expression comparing HRT users with nonusers [7]. Conversely, a prospective cohort study found combined HRT to be associated with tumors with amplification of HER2 receptor [13].

Table 4 Distribution of breast tumor characteristics among HRT users in relation to duration of HRT use

Tumor characteristics		Duration of HRT use n (%)		p value
		1<5 years *n*=76	≥5 years *n*=81	
Mitotic index	1	39 (53.4)	42 (51.9)	0.044
	2	11 (15.1)	24 (29.6)	
	3	23 (31.5)	15 (18.5)	

Table 5 HRT use and risk of breast tumor characteristics

Tumor characteristics		HRT users / HRT nonusers	OR[a] (95% CI)	OR[b] (95% CI)
Histologic type	Ductal	140/304	1.0	1.0
	Lobular	12/50	**0.5 (0.3–1.1)**	**0.4 (0.2–0.9)**
	Special type	3/14	0.6 (0.2–2.1)	0.5 (0.1–1.9)
Tumor size	≤ 20 mm	113/236	1.0	1.0
	21–50 mm	40/112	0.8 (0.5–1.2)	0.9 (0.6–1.5)
	> 50 mm	1/17	**0.1 (0.02–0.9)**	**0.1 (0.01–0.9)**
Histological grade	1	33/56	1.0	1.0
	2	74/153	0.7 (0.4–1.2)	0.8 (0.4–1.3)
	3	49/156	**0.5 (0.3–0.8)**	**0.5 (0.3–0.9)**
Mitotic index	1	81/138	1.0	1.0
	2	35/106	**0.6 (0.4–0.9)**	**0.6 (0.4–1.0)**
	3	38/120	**0.5 (0.3–0.9)**	**0.6 (0.3–0.9)**

Statistically significant results are shown **in bold**.

[a] Adjusted for age at diagnosis, years of OC use (never or <1, 1 <5, 5<10, 10 or more) and any first-degree relative with breast and/or ovarian cancer (yes, no).

[b] Adjusted for age at diagnosis, years of OC use (never or <1, 1 <5, 5<10, 10 or more), any first-degree relative with breast and/or ovarian cancer (yes, no) and recent mammography (yes, no).

The favorable effect of HRT use on tumor biology may not wane with time, as suggested by our finding that the mitotic index of score 2 was more often seen in long-term users, whereas score 3 in short-term users. Still, other tumor characteristics did not vary significantly by HRT duration as well as by regimen and route of administration, so further work is needed to address this issue.

In our study population, HRT users underwent more frequent mammography examinations. The difference in attendance of mammography examination at 2-year interval between HRT users and nonusers was huge, 87.1% vs. 56.6%. This might be explained by the fact that HRT users are required to obtain mammograms once per year as a prerequisite to continuing their HRT, whereas no such demand is placed on nonusers. Therefore, some authors have attributed a better prognosis among HRT users to earlier tumor detection by mammography. However, it should be noted that HRT use by increasing breast density might also reduce sensitivity and specificity of mammographic breast cancer screening [23, 24]. There is evidence that women who are currently using HRT are more likely than non-users to have breast cancer which presents in the interval between screens (interval cancer). Previous publications have also shown that women who are currently using HRT may experience more false positive recalls, whereby they are recalled for assessment after initial mammography, but are subsequently found not to have breast cancer. In other words, HRT might lead to both an increased as well as a decreased probability of early detection by mammography. Indeed, our data show that the favorable prognostic features among HRT users persisted even after adjustment for recent mammography. This demonstrates that the differences in outcomes in HRT users are more likely due to the development of less aggressive tumors than due to earlier detection by mammography.

The observation that HRT use is associated with tumors expressing a favorable prognostic profile might be explained by an influence of HRT on preexisting, clinically latent cancers [13, 25]. Breast cancers usually take more than 5 years to develop from early carcinogenesis to the clinical stage. Therefore, it is thought that hormones do not initiate new tumors, but may increase the likelihood of tumor growth during early stages of tumor formation, causing greater differentiation resulting in better outcomes. This potential explanation is supported by findings showing an increased risk only in current users and within a few years of hormone exposure, whereas 5 years after discontinuation of therapy, the risk returns to baseline.

In contrast to the reports from the observational studies, the WHI results in the estrogen-progestin arm indicated an earlier appearance of worse tumors. There are several reasons why the WHI data disagree with the bulk of data in the literature [25]. WHI participants were much older than the women normally experiencing menopausal symptoms. They were thus more likely to have preexisting tumors that became detectable after hormonal stimulation. Secondly, no nodes were examined in nearly 10%, and information on tumor size was missing in nearly 15% of the subjects who developed breast cancer. Because the number of incident cancers studied was small (199 in the treated group, 150 in the placebo group), a change in a few cases could have an impact on the conclusions.

Our study population was of medium size thus it is possible that some interactions were not significant due to insufficient number of subjects in HRT subgroups. The strengths of the study include the availability of information on potential confounders and the use of pathology reports at a single institution. This minimizes or precludes concerns regarding interinstitutional variations in IHC, FISH and other pathology results as well as their interpretation.

In the present study, we have shown that tumors arising in women taking HRT have a more favorable prognostic profile regardless of duration, regimen and route of administration. The beneficial tumor characteristics among

HRT users seem to be rather due to the development of less aggressive tumors through the influence of HRT on preexisting tumors causing their greater differentiation than earlier tumor detection by mammographic surveillance. These findings provide useful data when counseling patients on the risk and benefits of HRT use with respect to breast cancer.

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