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ORIGINAL ARTICLE

Impact of hormone replacement therapy on the histologic subtype of breast cancer

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Abstract
Objective Postmenopausal hormone replacement therapy (HRT) is associated with an increase in breast cancer risk, which correlates to the duration of HRT use. We wanted to investigate a possible association between HRT use and the risk of a histologic subtype of breast cancer.
Patients and methods From 1995 until 2004, 497 cases of primary ductal, lobular or ductulolobular breast cancer in postmenopausal women were diagnosed at the Department of Gynecology and Obstetrics, University Hospital Basel, Switzerland. The data was derived from patient's records. HRT ever use was defined as HRT use for ≥6 months.
Results Of the 99 cases of lobular cancer 72.7% were invasive lobular cancers, 21.2% were invasive ductulolobular cancers and 6.1% were lobular cancers in situ. Of the 398 cases of ductal cancer, 90.5% were invasive ductal cancers and 9.5% were ductal cancers in situ. Totally 144 women were HRT ever users, and 341 women were HRT never users. HRT status could not be defined in 12 women. HRT ever use was associated with an increased risk for lobular cancer (OR 1.67; 95% CI 1.02–2.73). Also, menopause due to bilateral oophorectomy was associated with an increased risk for lobular cancer (OR 2.42; 95% CI 1.06–5.54).
Conclusions There is evidence that HRT as well as menopause due to bilateral oophorectomy may be associated with an increased risk for lobular cancer. This association is of major clinical relevance, since lobular breast cancer is more difficult to diagnose clinically and radiologically than ductal breast cancer.

Keywords Breast cancer · Histologic subtype · Hormone replacement therapy (HRT)

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Introduction

Hormone replacement therapy (HRT) [51] is being used to treat menopausal symptoms caused by the falling levels of circulating ovarian hormones. Postmenopausal HRT is associated with an increased breast cancer risk that rises with the duration of HRT use [1, 4, 5, 16, 33, 45, 50], but dissipates after its discontinuation [1, 4, 13, 16, 33]. Breast cancer risk is no longer elevated 5 years after cessation of HRT, compared to women who never used HRT [1, 4, 13, 16, 33]. Combined estrogens–progestin HRT regimens increase breast cancer risk beyond the level associated with estrogens alone [1, 4, 14, 16, 36, 38, 41, 45].

Few previous studies have investigated a possible association between HRT use and the risk of a specific histological subtype of breast cancer with inconsistent conclusions: some studies report an elevated risk for lobular breast cancer in ever users of HRT [28, 30, 31, 34, 36], while others found no such association [47].

An increase in lobular breast cancer would be of clinical relevance since lobular breast cancer is less likely to be detected by mammography [6, 20, 22, 42, 44], ultrasound [6, 10, 44] or clinical examination [6, 10, 22, 25, 43] than ductal breast cancer. Additionally, HRT use is associated with an increase in breast density, a change which further hampers the diagnosis of breast cancer [8, 39].

Since diagnosis of lobular breast cancer is challenging, it is important to know if we should expect a higher incidence of lobular cancer in HRT users.

We conducted this hospital based case study to evaluate the relative risk for lobular breast cancer in current and ever HRT users in our patients.

Patients and methods

From 1995 until 2004, 661 cases of primary ductal, lobular or ductulolobular breast cancer were diagnosed at the Department of Gynecology and Obstetrics, University Hospital Basel, Switzerland. All women who were premenopausal (n = 164) by clinical assessment at the time of diagnosis were excluded. Totally 497 cases of postmenopausal ductal (n = 398) or lobular/ductulolobular (n = 99) breast cancer were eligible for this hospital based study.

Menopause was defined as the age of the last menstruation, or the age at bilateral oophorectomy. Women with unknown age of menopause due to premenopausal hysterectomy were considered as postmenopausal if breast cancer was diagnosed after the age of 52.

Ever HRT use was defined as transdermal or oral HRT use for ≥6 months. If the patient was on HRT for ≥6 months at the time of the diagnosis or ceased HRT ≤3 months before the diagnosis of breast cancer she was considered a current user.

The data considered for the current analysis derived from patient records, and if missing by telephone interview (n = 37). We collected data on menstrual, contraceptive and reproductive history; body size, weight, family history and personal history of invasive breast cancer or pre-invasive disease, as well as smoking, alcohol consumption, and history of diabetes. We obtained detailed information about the use, beginning, cessation, duration and brand of HRT. The institute of pathology of the University Hospital Basel provided all histological diagnoses and tumor characteristics.

Both established and suggested risk factors for breast cancer were included in the analysis as potential confounding factors, such as age at diagnosis, age at first birth, age at menopause, the type of menopause (natural, induced by bilateral oophorectomy, and unknown due to premenopausal hysterectomy), body mass index and family history of breast cancer.

Statistical analysis

In case of continuous parameters, t test or categorical variables, Fishers Exact Test was calculated to compare lobular against ductal cancer (Table 1).

Multiple logistic regression was performed (Table 2) to detect the influence of the parameters age at diagnosis, age at menopause, HRT, body mass index, family history as potential confounders and natural or induced menopause on the two histological subtypes of breast cancer. Odds ratios (OR) with corresponding 95% confidence intervals are reported for all these parameters.

In the case of continuous variables, odds ratio were expressed as the ratio of the odds from the 3rd to the 1st quartile of the corresponding distribution.

As body mass index and age at diagnosis show a skew distribution, a log transformation was applied. A P-value of <0.05 is considered as significant. All evaluations were calculated with SPSS Version 13.0.

Results

Of the 99 cases of lobular cancer 72.7% (n = 72) were invasive lobular cancer, 21.2% (n = 21) were invasive ductulolobular cancer and 6.1% (n = 6) were lobular cancer in situ. Of the 398 cases of ductal cancer 90.5% (n = 360) were invasive ductal cancer and 9.5% (n = 38) were ductal cancer in situ.

In our study we had 144 cases of breast cancer in HRT ever users and 341 cases in HRT never users. Among the ever users 109 were current and 35 were past users. In 12 cases HRT use remained unknown. The type of HRT (unopposed estrogen, estrogen plus progestin, tibolone and progestin) was comparable in ductal and lobular cancers (Table 1).

A comparison of lobular and ductal breast cancer cases is presented in Table 1 with respect to patients' and tumor characteristics.

Ever HRT use was associated with a significantly increased risk for lobular cancer OR 1.67 (95% CI 1.02–2.73). Surgical induced menopause due to bilateral oophorectomy was also associated with a significantly increased risk for lobular cancer OR 2.42 (95% CI 1.06–5.54). Age at diagnosis of breast cancer, family history for breast cancer, age at menopause, and body mass index showed no significant association to any subtype of breast cancer (Table 2).

All cases were included in the primary analysis. We also performed a subanalysis of invasive carcinomas excluding all in situ carcinomas. Bilateral oophorectomy remained associated with an increased risk for lobular cancer OR 2.32 (95% CI 1.01–5.33), whereas HRT ever use showed a trend towards an increased risk for lobular cancer OR 1.57 (95% CI 0.94–2.63). Another subanalysis was performed by excluding all women who had undergone premenopausal hysterectomy without bilateral oophorectomy. Bilateral oophorectomy showed an increased risk for lobular cancer OR 2.49 (95% CI 1.06–5.86), whereas HRT ever use showed no increased risk for lobular cancer OR 1.28 (95% CI 0.27–2.27).

Table 1 Patients' and tumor characteristics, and characteristics of menopause and hormone replacement therapy

	Ductal cancer (n = 398)		Lobular cancer (n = 99)		P
	Mean (n)	Min–max (%)	Mean (n)	Min–max (%)	
Patients characteristics					
Age at diagnosis of breast cancer (in years)	66.98	45–96	66.58	42–94	ns
Age at menarche (in years)	13.56	9–20	13.46	10–19	ns
Age at menopause (in years)	49.99	34–63	50.33	33–63	ns
Age at first birth (in years)	25.65	17–47	26.21	17–46	ns
Parity	1.62	0–6	1.71	0–5	ns
Family history of breast cancer					ns
Positive	87	21.9	31	31.3	
Negative	300	75.3	65	65.7	
Unknown	11	2.8	3	3.0	
Body mass index	25.89	16–42	25.83	19–40	ns
Alcohol consumption					ns
Never	163	41.0	43	43.5	
Regular	227	57.0	53	53.5	
Unknown	8	2.0	3	3.0	
Smoking					ns
Never	315	79.1	71	71.7	
Past or current smokers	77	19.4	25	25.3	
Unknown	6	1.5	3	3.0	
History of diabetes	42	10.6	9	9.1	ns
Tumor characteristics					
Tumor size					0.047
In situ	38	9.5	6	6.1	
pT1	183	46.0	37	37.4	
pT2	120	30.2	36	36.4	
pT3	19	4.8	12	12.1	
pT4	38	9.5	8	8.0	
Lymph nodes					ns
Negative	246	61.8	52	52.6	
Positive	143	36.0	44	44.4	
Nx	9	2.2	3	3.0	
Distant disease					ns
M0	371	93.2	90	90.9	
M1	23	5.8	9	9.1	
Mx	4	1.0	0	0.0	
Grading					0.005
1	86	21.6	8	8.1	
2	194	48.7	59	59.6	
3	118	29.7	32	32.3	
Estrogens receptor					ns
Positive	315	79.1	84	84.9	
Negative	77	19.4	13	13.1	
Unknown	6	1.5	2	2.0	
Progesterone receptor					ns
Positive	248	62.3	68	68.7	
Negative	144	36.2	29	29.3	
Unknown	6	1.5	2	2.0	

Table 1 continued

	Ductal cancer (n = 398)		Lobular cancer (n = 99)		P
	Mean (n)	Min–max (%)	Mean (n)	Min–max (%)	
Menopause and hormone replacement therapy					
Menopause					ns
Natural	286	71.9	68	68.7	
History of premenopausal hysterectomy without bilateral oophorectomy	92	23.1	21	21.2	
Menopause induced by bilateral oophorectomy	20	5.0	10	10.1	
Hormone replacement therapy					0.026
Never user	282	70.9	59	59.6	
Ever user	106	26.6	38	38.4	
Unknown	10	2.5	2	2.0	
Type of replacement therapy					ns
Estrogens plus progestin	50	47.2	20	52.6	
Estrogens monotherapy	54	51.0	15	39.5	
Tibolon	1	0.9	2	5.3	
Progestin	1	0.9	1	2.6	

Table 2 Multivariate analysis for factors influencing the histological subtype of breast cancer

	Ductal cancer	Lobular cancer	OR	95% CI
Age at diagnosis of breast cancer[a]	398	99	1.03	0.70–1.52
Family history for breast cancer	387	96	1.5	0.95–2.56
Age at menopause[b]	398	99	1.19	0.88–1.62
Body mass index[c]	398	99	1.03	0.75–1.41
Hormone replacement therapy[d]	388	97	1.67	1.02–2.73
Type of menopause[e]	398	99	2.42	1.06–5.54

[a] First quartile = 58, third quartile = 65

[b] First quartile = 47, third quartile = 53

[c] First quartile = 23, third quartile = 28.6

Reference groups

[d] HRT ever use, HRT never use

[e] Natural menopause (women with a history of premenopausal hysterectomy without oophorectomy included), menopause induced by premenopausal bilateral oophorectomy

Discussion

Breast cancer incidence seems to be stable or declining since 2003 [21, 35]. Up to 2003, however, breast cancer incidence had been rising in Western countries [24, 25], and there is evidence that this was more pronounced in lobular breast cancer than in ductal breast cancer.

Li et al. [24] reported a plateau in the incidence of ductal breast cancer, but an increase in the incidence of lobular breast cancer between 1987 and 1995 in the US. Two studies from Switzerland [23, 48] did not report a plateau, but an increased incidence rate in ductal (0.9–1.2% per year) as well as lobular (10–14% per year) breast cancer. The increase, however, was more substantial in lobular breast cancer. Furthermore, there seem to exist sharp differences in the incidence as well as in the histological subtyping of breast cancer between different European populations [49]. The rise of HRT use of 38–50% between 1987 and 1992 suggests an association between HRT use and increasing incidence of lobular breast cancer [5, 9, 18, 24].

Our data show an increased risk for lobular cancer in HRT ever users OR 1.67 (95% CI 1.02–2.73) and in women after bilateral oophorectomy OR 2.42 (95% CI 1.06–5.54).

In the primary analysis, where all cases were included, HRT ever use OR 1.67 (95% CI 1.02–2.73) showed a significant association with lobular cancer. Excluding all women with in situ carcinomas, a trend towards an increased risk for lobular cancer in HRT ever users OR 1.57 (95% CI 0.94–2.63) was seen. However, by excluding women who underwent premenopausal hysterectomy without bilateral oophorectomy, HRT ever users no longer showed an increased risk for lobular breast cancer OR 1.28 (CI 0.27–2.27). This might be explained by the fact that these women were usually estrogen HRT ever users.

Other studies are in agreement with our data [28, 31, 34, 36, 49]. Li et al. [24] also included in situ cancers in their analysis and reported an increased risk for lobular cancer

(OR 2.1; 95% CI 1.0–4.6), but not for ductal cancer. Likewise, the data of Newcomer et al. [34] showed an increased risk of lobular breast cancer (OR 1.5; 95% CI 1.1–2.1) in HRT ever users (estrogen alone and estrogen plus progestin), but not for ductal cancer.

Other authors reported an increased risk for ductal as well as lobular breast cancer, which was more pronounced for the latter [13, 17, 26, 33, 37, 45]. The pronounced risk of lobular breast cancer was seen after combined HRT (estrogen plus progestin) [17, 26, 33] and estrogen alone HRT, as well as after combined HRT in other studies [13, 37, 45]. In contrast, other groups did not find evidence that the effect of HRT was restricted to or more pronounced in lobular cancer [47].

While our data show a significant influence of surgical menopause by bilateral oophrectomy on the incidence of lobular breast cancer [OR 2.42 (95% CI 1.06–5.54)], only a statistical trend was seen in the work of others [27]. Excluding all women with in situ carcinomas OR 2.32 (95% CI 1.01–5.33), and all women who underwent premenopausal hysterectomy without bilateral oophorectomy OR 2.49 (CI 1.06–5.86) bilateral oophorectomy remained associated with an increased risk for lobular cancer. HRT is frequently prescribed to reduce menopausal symptoms caused by premenopausal bilateral oophrectomy. Therefore, these women take HRT earlier in life, and for a longer period.

Substantial methodological differences between the studies analyzing the effects of HRT and certain subtypes of breast cancer make a comparison of the data very difficult. Some authors restricted the age of women included in the studies to 65 years [17, 28, 31], whereas we and others include also elderly women [13, 26, 34, 37]. Some studies compare invasive ductal to lobular cancers [34] while others compare lobular to nonlobular cancers [13] or ductal to lobular and to tubular cancers [37]. As in the presented data lobular and ductulolobular cancers are compared to ductal cancers [17] and in situ cancers are included in the analysis [28]. In agreement to our study some authors define HRT use if HRT was used for ≥6 months [13, 28], while others define it as ≥3 months [34]. Many studies do not define HRT use at all.

A shortcoming of our study is the relatively small number of breast cancer cases in HRT ever users and the small number of lobular cancers. The charts did not contain structured questionnaires, and missing data were obtained by telephone interview.

In spite of the relatively small numbers of breast cancer cases in our cohort study, the presented data add to the growing evidence that HRT might be associated to lobular breast cancer. This association is of major clinical relevance, since lobular breast cancer is more difficult to diagnose than ductal breast cancer.

Invasive lobular breast cancers are distinguished histologicaly from infiltrating ductal carcinomas by their diffusive infiltrative pattern that does not destroy the anatomic structures. They often fail to form distinct masses due to the lack of a desmoplastic reaction which prevents the lesions from being clinically and radiologically detected.

As a result, the sensitivity of a physical examination, including mammography and ultrasound to detect lobular breast cancer is lower than for the more common ductal breast cancer [2, 10, 22, 43, 44]. This is also shown by our data since lobular breast cancer tends to be larger in size than ductal breast cancer at diagnosis.

Subtle changes that may mimic normal breast parenchyma, including opacity similar to that of normal fibroglandular tissue, as well as the common lack of suspicious microcalcifications are reasons for the high rate of up to 19% false-negative mammographic diagnosis [6, 20, 22, 39, 42, 44, 52]. In up to 8%, mammograms may even be completely normal in lobular breast cancer [20, 42, 44].

While ultrasound seems to be more sensitive in detecting lobular breast cancer than mammography, a false negative rate of 12.3% has been reported. [6, 10, 20, 42, 44].

HRT increases mammographic breast density and decreases the sensitivity and specificity of mammography [3, 8, 12, 15, 19, 29, 39] further leaving breast cancer undetected [3, 6–8, 11, 12, 15, 32, 39, 40, 46].

Equivocal clinical, mammographic or sonographic findings in the breasts of women with a history of menopause induced by oophorectomy, or in past or current HRT users should lead to further investigations to exclude lobular breast cancer.

Our data show an increased risk for lobular breast cancer in ever HRT users and in patients with a history of menopause induced by bilateral oophorectomy. This is relevant since lobular breast cancer might pose a diagnostic challenge.

Conflict of interest No conflicts of interest to declare.

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