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Hormone Replacement Therapy After Breast Cancer

A. O. Mueck¹, T. Rabe², L. Kiesel³, T. Strowitzki²

*So far, patient samples in all studies investigating hormone replacement therapy (HRT) after breast cancer have been small. Therefore, HRT should only be used if alternatives such as specifically not contraindicated phytopreparations or selective serotonin reuptake inhibitors (SSRIs) are not effective. This is primarily due to forensic reasons since clinical data on the risk of alternatives (based on present evidence) are even more sparse. Regarding HRT, four prospective randomized studies and at least 15 observational studies after breast cancer are available. Only the HABITS study shows an increased risk of relapse. The authors suggest that this is probably associated with the relatively high number of patients with HRT treatment after ER-positive cancers as well as due to the preferred use of estrogen/progestin-combined preparations. Based on the results of the randomized placebo-controlled study Women's Health Initiative (WHI) as well as of at least 12 observational studies, the progestin component seems to be mainly responsible for the probability of increased diagnosis frequency of primary breast cancer. However, no data are available on the impact of progestin on the use of combined HRT after breast cancer. However, also with estrogen only an increased risk of relapse must be expected and patients should be informed about it. This has to be concluded due to biological plausibility and observational studies although the estrogen-only arm in WHI did not show any increased primary risk. Thus, any form of HRT should only be performed in exceptional cases, and treatment duration should be as short as possible with the lowest effective dose. **J Reproduktionsmed Endokrinol 2008; 5 (2): 83–92.***

Key words: breast cancer history, hormone replacement therapy, HRT, alternatives to HRT

In the USA, most of the 2.5 million women who have undergone surgery for breast cancer are postmenopausal. Furthermore, 25 % of the 180,000 women who are diagnosed with breast cancer annually are of a reproductive age. 70 % of these women have suffered premature menopause as a result of adjuvant chemotherapy [1]. Consequently, after primary treatment for breast cancer, these women suffer from menopausal symptoms, such as hot flashes, mood disorders, sleep disturbance, concentration difficulties, and sexual dysfunction, which may reduce their quality of life [2, 3]. Hormone replacement therapy (HRT) is the most effective treatment for symptoms of the climacteric, which often occur in a particularly pronounced form after breast cancer.

In addition, menopause increases the risk of osteoporosis [4]. HRT brings about an improvement in menopausal symptoms [5], protects against osteoporosis [6], but appears to be associated with an increased probability of a diagnosis of breast cancer in women with no previous history of breast cancer. The risk of breast cancer relapse in women after primary treatment for the disease is, however, as yet unclear. The question is even more relevant due to the fact that many women who have suffered from breast cancer are interested in

using HRT due to its short- and long-term advantages [3, 7].

Breast cancer is listed as a contraindication for all HRT preparations, including tibolone. There are no results from placebo-controlled studies regarding the use of HRT after breast cancer. The intention of this overview is to estimate the risk based on the available open studies, as well as experimental data and theoretical considerations and to give practical recommendations considering the forensic situation as well.

Rationale for Increased Breast Cancer Risk Caused by HRT

Breast cancer is the most common cancer in women. Approximately 75 % of women affected are postmenopausal at the time of diagnosis; of those who are premenopausal, approximately 70 % will be permanently amenorrhoeic as a result of treatment. Therefore, many women are exposed to the consequences of estrogen deficiency.

The risk of HRT is explained by the fact that decisive strategies in treatment after breast cancer aim to have an anti-estrogenic effect: tamoxifen reduced the risk of contralateral breast cancer in women with a history of breast cancer [8] and halved

the risk of breast cancer in women at increased risk of the disease [9]. Even better results are emerging for the use of sequential, or possibly also the primary, use of aromatase inhibitors [10].

These strategies function primarily as estrogen antagonists in the breast, tissue and metastases, where estrogen production is mostly considerably higher than in the blood. The significance of a comparatively very small increase in the peripheral estradiol level with HRT remains unclear, as estradiol cannot be actively transported against a concentration gradient from the blood into the breast or metastases. In contrast, it is known that prophylactic ovariectomy can also reduce the risk of breast cancer [11–13] – the precursors required for peripheral estradiol biosynthesis in the target organs, especially the breast, are removed here, and also a battery of much more powerful growth and promotion factors (when compared to estradiol). As a result, there is an array of approaches to explain the primary breast cancer risk under HRT, more precisely the probability of an earlier diagnosis, and also other effects, such as the metabolic effects of insulin metabolism [14].

Because the data available on both effects and valid clinical studies re-

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Table 1. Observational studies of HRT use in women with a history of breast cancer

Studies (author)	n _{tot} /n ¹	Mean age (years)	Stage	Lymph node status		ER/PR status	Mean DFI before HRT start (months)	Mean duration of HRT use (months)	Mean follow-up after HRT start (months)	Recurrence
				neg.	pos.					
Controlled										
Eden 1995 [15]	90/90	47 ²	NR	72	18	12 ER+ 10 ER– 68 unknown	60 ²	18 ²	24 ²	6
Beckmann 1998 [16]	64/64	NR	37 T1 19 T2 8 T3/T4	44	20	31 ER+ 33 ER– 34 PR +30 PR–	0	15	32	6
Ursic-Vrscaj 1999 [17]	21/21	47 ¹	1 Stage I 12 Stage II 8 Stage III	14	7	NR	62	28 ³	28	4
Vassilopoulou-Sellin 1999 [18]	39/39	45 ¹	8 tumours < 1 cm 21 tumours 1–3 cm 9 tumours > 3 cm 1 occult tumour	21	15	29 ER– 10 unknown	114	40 ⁴	40	1
Total	214	45 ⁵	N/A	151	60	N/A	52 ⁵	22 ⁵	30 ⁵	17
Uncontrolled										
Wile 1993 [19]	25/23	51	2 Stage 0 13 Stage I 7 Stage II 1 Stage III 2 unknown	15	1	13 ER+ 3 ER– 9 unknown	26	35.2	35.2 ³	3
Powles 1993 [20]	35/35	51	12 T1 14 T2 9 T3	12	10	NR	31	14.6	14.6	2
DiSaia 1995 [21]	77/71	50	6 Stage 0 43 Stage I 17 Stage II 5 Stage III 6 unknown	58	13	20 ER+/PR+ 8 ER+/PR– 3 ER–/PR+ 9 ER–/PR– 37 unknown	23.8 ²	27 ²	35.2 ²	7
Decker 1996 [22]	61/45	52	16 TisN0M0 23 T1N0M0 20 Tx-2N1M0 2 T3-4N1M0	39	22	15 ER+/PR+ 1 ER+/PR– 4 ER+/PR? 3 ER–/PR+ 15 ER–/PR– 2 ER–/PR? 21 unknown	44.4	26.4	26.4 ³	5
Peters 1996 [23]	56/42	NR	14 Stage 0 26 Stage I 14 Stage II 2 unknown	40	0	19 ER+/PR+ 5 ER+/PR– 3 ER–/PR+ 6 ER–/PR– 23 unknown	57	37 ⁴	37	0
Bluming 1999 [24]	189/132	NR	57 T0N0 87 T1N0 16 T2N0 19 T1N1 9 T2N1	160	29	99 ER+ or PR+ 90 unknown	59 ²	41 ²	41 ^{2,3}	12
Espie 1999 [25]	120/107	45	71 T0–T2 44 T35 T4	72	48	80 ER+	96 ²	28.8 ²	28.8 ^{2,3}	5
Total (all)	669	49 ⁵	N/A	547	183	N/A	56 ⁵	30 ⁵	33 ⁵	51
n _{tot} : total number of patients; NR: not reported; N/A: not available; ER: estrogen receptor; PR: progesterone receptor; DFI: disease-free interval; ¹ DCIS patients excluded; ² mean value; ³ correlate to HRT duration of use; ⁴ equals mean follow-up duration after HRT start; ⁵ weighted average										

n_{tot}: total number of patients; NR: not reported; N/A: not available; ER: estrogen receptor; PR: progesterone receptor; DFI: disease-free interval;
¹ DCIS patients excluded; ² mean value; ³ correlate to HRT duration of use; ⁴ equals mean follow-up duration after HRT start; ⁵ weighted average

mains unclear, the greatest reservation still concerns the use of HRT in women with a history of breast cancer. Women with menopausal symptoms after breast cancer remain the greatest problem group regarding a potential indication for HRT – basically this must be considered without fail in the light of the following

summary of the currently existing studies!

Observational Studies

Observational studies performed on HRT after breast cancer were partly uncontrolled, and partly carried out

as unblinded case/control studies. The observational studies performed are shown in Table 1, for which the clinically relevant data from the respective publications are shown.

As the table shows, they vary greatly with respect to the HRT used, duration of treatment, and follow-up. De-

Table 2. Annual relapse rate in observational studies with HRT after breast cancer – quantitative risk calculation (modified from [26])

Study	HRT	control	RR	95 %-CI
Controlled studies				
Eden [15]	0.033	0.091	0.40	0.17–0.93
Beckmann [16]	0.035	0.057	0.67	0.28–1.61
Ursic-Vrsaj [17]	0.082	0.054	1.60	0.48–5.34
Vassilopoulos-Sellin [18]	0.008	0.015	0.51	0.07–3.79
Total¹	0.034	0.063	0.64	0.36–1.15
Uncontrolled studies²				
Wile [19]	0.044	0.033	1.5	0.28–8.16
Powles [20]	0.047	0.042	1.0	0.15–6.71
DiSaia [21]	0.034	0.033	1.17	0.41–3.30
Decker [22]	0.051	0.041	1.25	0.36–4.35
Peters [23]	0	0.024	0.11	0.01–2.68
Bluming [24]	0.027	0.026	1.09	0.50–2.38
Espie [25]	0.019	0.034	0.63	0.21–1.85
Total	0.30	0.042³	0.82	0.58–1.15

RR: Relative Risk; CI: Confidence interval

¹: weighted mean; ²: for control group of recurrence rate estimated, adjusted for disease-free interval and nodal status (Disease-Free Interval, DFI); ³: Combined data of four controlled trials and seven studies with estimated recurrence rates of the control group

spite these limitations, Col et al [26] performed a first quantitative evaluation on the basis of 4 controlled and 7 further observational studies (Tab. 2). An increase in the relapse rate as a result of HRT was not substantiated by any of these studies.

In detail, in this analysis of 11 studies only 4 had adequate control groups [15–18]. In order to calculate the relative risk of breast cancer relapse (defined as new breast cancer) in the 7 uncontrolled studies [19–25], 7 control groups were generated by the authors. The expected number of relapses was estimated with the same sample size for each hypothetical

control group, and in doing so the disease-free interval and the lymph-node status of the HRT user was included in each study.

The 4 studies with control groups included a total of 214 women who had undergone primary treatment for breast cancer, and had received HRT for an average of 22 months (Tab. 1). Two of these studies had no defined exclusion criteria [15, 16], one study excluded women with a ductal carcinoma in situ (DCIS) [17] and in another study, only menopausal women with a tumour stage I or II and a minimum of a 2-year disease-free interval (when estrogen receptor (ER) negative) or 10-year disease-free

interval (in the case of unknown estrogen receptor status) were included [18]. Almost 80 % of these women were of tumour stage I or II at first diagnosis and more than 70 % were node-negative. At least 20 % were estrogen receptor-positive and 16 % progesterone receptor-positive. The mean disease-free interval was 52 months and the mean follow-up after initiation of HRT was 30 months.

The evaluation of the 4 studies with control groups gave an annual relapse rate of 4.2 %, with a range from 1–8 %. During the observational period, 17 (8 %) of the 214 HRT users incurred a relapse. Relapse occurred in 66 (11 %) of the women in the group who did not take HRT after primary breast cancer. The combined relative risk (RR) of a relapse in connection with HRT was 0.64 (Fig. 1). This result was not significant (95 %-CI 0.36–1.15).

A main limitation in the analysis of these 4 studies is that only few data were presented for the control groups. Any comparisons in terms of important breast cancer risk factors are mostly missing as well as more explicit descriptions on hormonal pre-treatments. Thus, apart from the small case numbers it seems not to be adequate to draw conclusions from these studies or this analysis.

For the analysis of all 11 studies, a total of 669 women, who received HRT after breast cancer, could be evaluated, with a mean treatment duration of 30 months. Their clinical characteristics do not distinguish

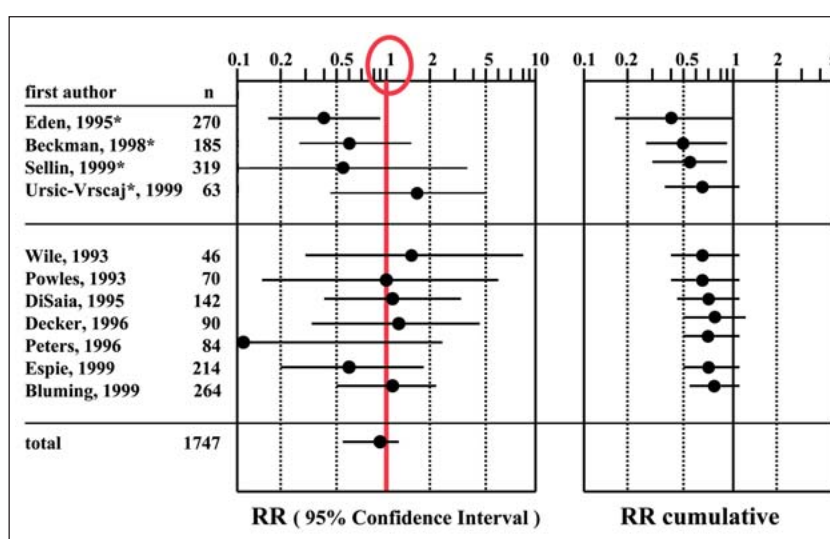


Figure 1. Relative risk of breast cancer relapse in connection with HRT – quantitative risk calculation (modified from [26]).

Lines: 95%-Confidence interval

*Studies with control groups. Left side shows data from each single study, right side represents a cumulative meta-analysis.

them greatly from the women in the 4 studies with a control group (Tab. 1). With the enlistment of a virtual control group in the 7 studies without control group, the relative risk (RR) was 0.82 (0.58–1.15). The disease-free interval was inversely correlated to the relapse rate of HRT users.

Treatment Examples of Individual Observational Studies

None of the studies to date can be used as evidence that HRT after breast cancer might not lead to increased breast cancer risk. For example, in a German study, after approximately 3 years Beckmann et al [16] found significantly fewer deaths with HRT after breast cancer compared to their well-matched and control group described in detail (6 vs 13 %). However, they remark that such treatment must remain an individual case decision. Performing such observational studies can, however, give practical suggestions, under which terms and how in the case of such special decisions HRT could be used, in the optimal case in the scope of studies.

Especially well known is an Australian study that is characterized by its extended collective, and still running and has also been published in follow-up analyses. In the primary case/control study [15], 90 patients were treated with combined HRT after a relapse-free interval of 5 years after breast cancer and compared with 180 patients without HRT, who had

similar tumours according to all relevant parameters. With HRT, relapse occurred in 7 % after a mean of 1.5 years, and in 17 % without HRT (RR 0.4). No deaths occurred in the HRT group during the observational period, but 6 % of patients in the control group died. For receptor-positive tumours there was no increased tendency towards relapse, however, the receptor status was only known in 24 % of the patients. The study was carried on in the style of a cohort study [27]. In a comparison of 167 patients using HRT with a cohort of 1472 women with breast cancer, there was an (albeit not significant) risk reduction of 33 % for combined treatment (91 %).

We refer to one of the most recent (still ongoing) observational studies which attempts to organise and carry out a maximally optimised “nested” case/control study: in the study by O’Meara et al [28], 2755 women between the ages of 35–74 years were included, in whom invasive breast cancer had been diagnosed between 1977 and 1994. 174 HRT users were identified after diagnosis. Each “HRT user” was compared to 4 randomly chosen “HRT non-users” of the same age, same tumour stage and year of diagnosis. The primary aim of the study was to determine the incidence of breast cancer relapse in HRT versus “non-HRT” users after breast cancer.

The results of this study showed a breast cancer relapse rate of 17 per 1000 women-years for women who used HRT after being diagnosed with

breast cancer and 30 per 1000 women-years for the so-called “non-users” (RR = 0.50; 0.3–0.85). The rate of breast cancer mortality was 5 per 1000 women-years in the HRT user group and 15 per 1000 women-years in the group without HRT (RR = 0.34; 0.13–0.91). The total mortality rate was 16 per 1000 women-years in the HRT group and 30 per 1000 women-years in the group without HRT (RR = 0.48; 0.29–0.78). The reduced incidence of breast cancer relapse or death was observed in women using all forms of HRT (only oral HRT use = 41 %; only vaginal use = 43 %; oral and vaginal = 16 %). No indication of a risk reduction with increasing dose was found.

Prospective Randomised Studies

For all observational studies mentioned it cannot be excluded that mostly women with a favourable prognosis and appropriate menopausal symptoms opted for HRT. This “selection bias”, common in observational studies, occurs frequently in the medical history of women with breast cancer, who do not uncommonly associate their illness directly with earlier HRT – hence prospective randomised studies have a particular relevance with regard to this question, but then again, they are particularly difficult to carry out for the same reason.

At present, only 4 prospective randomised studies are known (Tab. 3) [30–32, 34], of which 2 Swedish

Table 3. Prospective randomised studies on HRT use in women with a history of breast cancer

First author (year)	n (HRT)	Stage	HRT type	Mean duration of use (months, range)	Mean follow-up (months, range)	Recurrence ¹	Deaths ¹
Marsden (1997, 2000) [29, 30] ²	51	n/a	n/a	6	n/a	2	n/a
Vassilopoulou-Sellin (2002) [31] ³	56	I–II	Only E	71 (61–128)	n/a	2	0
Holmberg (2004) [32] ⁴	174	I–II	E (21 %) SHRT (26 %) CCHRT (46 %) G etc (6 %)	25.2 (1–64)	> 60 planned, early abrupted	26	3
von Schoultz (2005) [33] ⁵	175	I–IV	E (23 %) SHRT (22 %) CCHRT (0 %) SIHRT (50 %)	49.2 (2–84)	> 60 planned, early abrupted	11	2

E: Estrogen only; G: Progestins only; CHRT: combined HRT without further information regarding of progestine type and therapeutical regimen; SHRT: Sequential Combined HRT; CCHRT: Continous Combined HRT; SIHRT (Stockholm Study) Sequential Interval Therapy = 69 days E, followed by 14 days E+P, followed by 1 week free interval (cycle 90 d.); n/a: not available

¹: relapse and deaths due to breast cancer in HRT users; no significant difference when compared to the controls in studies with control groups (no increase in risk), including the significant increase recurrence risk in the habit study, see text; ²: ongoing prospective randomized study, pilot study closed, until yet, no further information; ³: Case-control study (n = 56/243), partially randomized (n = 34/43); ⁴: only study with increased recurrence risk (see text); ⁵: early withdrawal due to problems with recruitment after stop of the habit study (see text).

studies were prematurely terminated [32, 34]. One English study is still designated as a pilot study by the authors on the grounds of ongoing recruitment problems, although it was planned and designed almost 10 years ago and officially began nearly 5 years ago [29, 30]. Hardly any information is available for this study (Tab. 3).

The Swedish HABITS (Hormonal replacement therapy After Breast cancer – Is it Safe) study is, on the whole, currently termed the most important study after breast cancer [32] – primarily because it is the only study to show an increased risk of relapse with HRT. HABITS was designed as an open randomised study with women who had suffered breast disease, and who had received either HRT or non-hormonal treatment. The primary study end point was relapse. Recruitment began in 1997; 434 women were randomised up to September 2003; 345 had at least one follow-up examination ($n = 174/171$). After a mean follow-up of 2.1 years an increased risk was found with HRT use after breast cancer (RH 3.3; 95 %-CI 1.5–7.4)! 26 women using HRT (14.9 %) as opposed to only 7 in the control group (4.1 %) suffered a relapse; breast cancer mortality was not increased (1.7/2.3 %). On the grounds of this study data, the study was terminated on December 17, 2003 [32].

A study carried out in parallel in Sweden showed opposing results, i.e., more favourable data for HRT users [33]. Despite the fact that this second, simultaneously performed study (also a prospective randomised Swedish trial, the “Stockholm Study”, SS), with a Relative Hazard (RH, equivalent to Relative Risk, RR) of 0.82 (0.35–1.9) and an inclusion of 175/184 women, showed no increase in risk, even with the duration of treatment being twice as long (mean 4.1 years), it was also prematurely terminated. The reason were recruitment problems, and not – as repeatedly incorrectly stated – the risk increase occurring as a result of the pooling of data from both studies (1.8; 95 %-CI 1.03–1.9). Assessment of the heterogeneity of both studies shows significant differences, due to medical history data, study terms and above all, the choice of HRT. As the authors point out, both studies

should not be pooled, but evaluated separately.

The authors surmise that a risk increase was avoided because the progestogen supplement in the SS was altogether minimised. In comparison, the proportion of estrogen therapy and sequential HRT was almost identical (HABITS/SS 21/23 % and 26/22 %). Continued progestogen supplementation was allowed, however, in HABITS (46 %), whereas in SS, women < 55 years were only treated with progestogen supplementation (50 %) every 3 months. The HRT used was only defined in SS (estradiol valerate, MPA); however, it is completely unclear to what extent various hormone components could determine the varying risks. Yet the adjuvant tamoxifen treatment, which was twice as common (52 %) in SS, is considered to be important since, according to the Italian Tamoxifen Prevention Study, tamoxifen can reduce an estrogen-related risk increase [35].

In addition to HABITS and the Stockholm Study, the study by Vassilopoulou et al [31], also listed in Table 2, seems to be remarkable, and is so far the only at least partly randomised, prospective case/control study. Treatment was carried out with estrogen, without progestogen supplementation, and solely for women after localised stage-I or -II breast cancer with a disease-free interval of at least 2 years, and only after ER-negative cancer or no less than a 10-year interval in the case of unknown receptor status. HRT was given over a mean of 71 months; no increased risk of relapse was found. In our opinion, this study can serve as an example in its construction and implementation of how one can use short-term HRT in individual cases as an exception. According to the above discussion, it is advisable to minimise the duration of progestogen supplementation, for example only every 3 months, or to give interval therapy determined by the results of vaginal sonography. According to the data currently available, with regard to the primary risks it is possibly advisable to prescribe micronised progesterone (oral or vaginal) – only after appropriate explanation to the patient regarding the “off-label” use of HRT.

Tibolone After Breast Cancer

Tibolone as well as conventional HRT is also used for the successful treatment of menopausal symptoms, and is supposedly also comparably effective for the prevention of osteoporosis. The essential difference, also in comparison to Selective Estrogen Receptor Modulators (SERM) such as raloxifen, is that tibolone is a pro-drug, i.e., is degraded to active metabolites. This can therefore account for its differing “tissue-selective” effects according to the Selective Tissue Estrogenic Activity Regulator (STEAR) principle, as various enzyme systems are regulated differently according to metabolite quantity and spectrum, which consequently regulate the ligands on the estrogen receptor. According to the results of experimental tests, the delta4-isomer metabolite is especially active in the breast and in most experimental tests, anti-proliferative as well as pro-apoptotic effects have been demonstrated.

However, it cannot be concluded that the use of tibolone for breast cancer or relapse prevention is without risk. It is possible that the desired metabolism does not take place or is insufficient in certain individuals (e.g., as a result of a genetic polymorphism of the key enzyme) [36]. But this would influence primary breast cancer risk and perhaps not the relapse rate, and it remains unanswered to what extent this can explain the observed increased incidence of primary breast cancer diagnoses in the English “Million Women Study” at the moment, because it is known that tibolone is preferred in England (also) for use in at-risk patients [36]. It is certain that mammographic density is only rarely increased under tibolone therapy, and the risk of interval carcinoma can be reduced [37]. In the framework of an international consensus statement published in 2005, however, the safety of tibolone for breast tissue was given the evidence grade “non-conclusive” with the reasoning: “randomised controlled studies investigating breast cancer incidence and tibolone must be awaited before a substantiated conclusion can be drawn” [37].

The Livial Intervention following Breast cancer; Efficacy, Recurrence

And Tolerability Endpoints (LIBERATE) study, which specifically focuses on the use of tibolone after breast cancer, was begun in 2002. LIBERATE is a randomised, placebo-controlled study investigating the efficacy and tolerability of tibolone in patients with breast cancer and concurrent menopausal symptoms. The study, including more than 3000 patients, was completed in December 2007. In the most recent review of the unblinded data, the Data Safety Monitoring Board (DSMB) found a trend towards an increased incidence of breast cancer relapse in women who had received tibolone. Although the anomaly did not reach the predefined limit of "proof beyond reasonable doubt", it appears highly unlikely to the DSMB that the criteria for a non-inferiority of tibolone vs placebo can still be achieved. Consequently, a continuation of the LIBERATE study is no longer considered beneficial on statistical grounds. Based on the results of the DSMB analysis, the LIBERATE Advisory Board has advised Organon that the study medication be appropriately stopped and the study be brought to a close. Organon followed the recommendation that the patients stop the study medication as soon as possible and have their last study visit by July 31, 2007, at the latest.

The first results of the statistical analyses of the LIBERATE trial were recently presented during the 12th World Congress on the Menopause in Madrid (Spain) from May 19–23, 2008. The analysis was announced in the abstract book [38], evaluating 3148 patients, mean age at randomization 52.6 years, mean time since surgery 2.1 years, mean daily number of hot flushes and sweating episodes 7.2 and 6.1, respectively. The primary tumour was N+ for 58 % of the patients and ER+ for 78 %. Prior to or at study entry, tamoxifen was given to 75 % of the patients and aromatase inhibitors to 8 %. The results have not yet been published, but according to the congress presentation a significant increase of breast cancer recurrence in the tibolone group compared to placebo with HR 1.40 (1.14–1.70; $p < 0.001$) was confirmed. In further analyses, special attention will be given to various subgroups of patients [39].

According to these data, it does not appear justifiable to offer tibolone as first-line treatment for menopausal symptoms after breast cancer. A history of breast cancer will remain a contraindication for tibolone use according to the package insert. Therefore, before tibolone is prescribed, an explanation should be offered to the patient, exactly as for estrogen/progestogen preparations, and must be documented in the patient's medical record in a legally valid way. The decision to prescribe tibolone currently remains a decision to be made for each individual case.

Further Studies with HRT After Breast Cancer Are Required

With the exception of the LIBERATE study, the number of patients in all studies were too small to answer the question of risk. Case number estimates show that in a follow-up period of 5 years, a total of 1300 women must be reviewed to prove with 80 % statistical power that there is no increased risk (5 %-level of significance). HABITS [32] and the Stockholm Study [33] should have been carried out on this basis, but were unfortunately prematurely terminated.

The consequence must not be to no longer further investigate certain HRT regimens after breast cancer. Too high is the psychological strain for the 75 % of women with severe vasomotoric and urogenital symptoms, which can too commonly be successfully treated simply with HRT. On the basis of the results, it would be justifiable to further investigate low-dose estrogens. The significant risk increase in HABITS, only for ER-positive, not for ER-negative patients, only for women without, not with tamoxifen treatment, as well as for women already treated with HRT, also indicates how risks can possibly be reduced.

Risk Assessment According to Primary Breast Cancer Incidence and Biological Plausibility

The most important consequence of the data available should be to minimize progestogen supplementation, especially in high-risk women. The differing results from the WHI study were already groundbreaking, and

the study was the only placebo-controlled randomised intervention study to establish a risk of primary breast cancer with HRT. It is generally known that an increased risk of breast cancer was only seen in the combined arm, and only in women treated with HRT before the start of the study [40]. The risk was (non-significantly) reduced by 23 % in the estrogen monotherapy arm – a result which must be investigated in further studies on the basis of its relevance [41]. Approximately 50 observational studies have shown an increased, reduced or no risk.

If there is a real risk with estrogen monotherapy, then it cannot definitely be proven on the basis of statistical analyses from studies. In the large Oxford Reanalysis of 50 studies, an increased risk was shown. This, however, was ultimately based on a few special American studies [42], a risk which was not confirmed in the last analysis by Trudy Bush (considered to be the most competent epidemiologist in the field of HRT and died of breast cancer in 2001). Her analysis was performed on the basis of 45 studies carried out between 1975 and 2000 [43], and furthermore, after adequate adjustment, no increased risk was found in the recent meta-regression analysis of the relevant total of 39 studies from the Oxford analysis [44]. On the other hand, in the most recent meta-analysis, an increased risk of breast cancer diagnosis with estrogen therapy was once again shown [45], yet the methodologically controversial Million Women Study [46] fundamentally defined the statistics.

The risk in the respective collectives investigated presumably depends on the amount and type of existing malignant cells and the potential to block them. A causal relationship between breast cancer development and HRT has never been proven. Currently, however, 13 observational studies as well as the WHI argue that progestogens can increase the risk [47], and from our own investigations, most notably by activation of stromal growth factors and alteration in the metabolism of estrogens, induced by special progestogens [48, 49]. The results for malignant cells may not be conferred onto healthy cells (and vice versa), because the progestogen effects are partly dia-

metrically different. This should be borne in mind, as one-sided investigations are often drawn upon as apparent confirmation of the safety of preparations, such as for example, breast epithelial cell proliferation by means of fine needle biopsy. On the other hand, data regarding breast cell apoptosis should also be taken into account [50, 51].

Regarding possible mechanisms increasing the primary risk of breast cancer it should be pointed out that the WHO recently classified combined HRT as well as oral contraceptive preparations as "carcinogenic" [52]. According to the opinion of 6 authoritative gynaecological associations in Germany, this classification remains according to pure pharmacological criteria, without practical consequences, primarily because of the lack of information about absolute and relative risks [53]. This is especially true for the primary use of steroid hormones. For use after gynaecological tumours such as prior breast cancer, the question of the mechanisms with a possible causal link is naturally particularly interesting, but still open.

The possible proliferative effects described above have been proven. It was recently shown (once again!), on the basis of pathobiological tumour cell calculations, that in studies with a duration of less than 5–10 years, no causal link could exist because no breast tumour can reach the necessary size of at least 0.5 cm needed for a clinical diagnosis within this time [54]. To what extent the accumulation of potential specialised genotoxic estrogen metabolites can cause malignancies needs to be clarified – up to now there are only experimental indications [51, 55]. Only clinical studies can ultimately answer the question of risk. As long as causal relationships are not proven, a risk evaluation from studies should always be referred to as "risk for an increased possibility of diagnosis" rather than risk of breast cancer per se.

Alternatives to HRT

Although no treatment principle has proven more effective than HRT for the primary prevention of osteoporosis after surgical menopause or early after natural menopause, for exam-

ple, raloxifen or bisphosphonates, essentially with calcium and vitamin D supplementation should be used in the prevention of osteoporosis in the specific high-risk group of patients after breast cancer. Vaginal discomfort, which is very common after primary treatment of breast cancer, can be treated locally. However, it must be borne in mind that breast cancer is listed as a contraindication for local estrogen application, including estriol – an adequate explanation with an entry in the patient's medical records should follow accordingly. The recommended dose listed should be strictly adhered to, otherwise systemic effects can be expected. Such effects are definitely proven for the vaginal ring, which has the indication of a local estradiol treatment.

According to the latest position statement of the German Society for Senology (Deutsche Gesellschaft für Senologie), menopausal symptoms should first be treated with antidepressants such as paroxetine or fluoxetine (SSRIs) and venlafaxine (selective serotonin-noradrenaline reuptake inhibitor, SNRI), because they have shown good efficacy in controlled studies [56]. They can, however, cause significant side effects, such as nausea, constipation, dry mouth, gastrointestinal bleeding as well as central effects. A current warning repeatedly given by the German Drug Commission is an increased risk of suicide – certainly a particularly serious matter when treating patients after cancer! Furthermore, a reduction in the concentration of the main tamoxifen metabolites of at least 50 % has been seen in women with breast cancer who were taking paroxetine [57].

Regarding alternative therapy with phytoestrogens there is a controversial discussion about the clinical importance of the 3–4-fold stronger binding of isoflavones to the estradiol receptor- β as compared to binding to estradiol receptor- α , because ER- β is believed to exert antiproliferative activities on breast epithelial cells. However, according to new in vitro and in vivo tests, isoflavones, for example from red clover or soya preparations, can depend on the mixture of the different substances (including biologically active metabolites) and depend on the concen-

trations that also elicit proliferative effects in the breast. Moreover, these preparations can also diminish or abolish the protective effect of tamoxifen due to animal experimental data [58].

Those negative effects are not known with *cimicifuga* preparations which elicit their different biological effects not via estrogen receptors but rather by central nervous effects influencing serotonin receptors although the exact mechanisms are still unclear. At least 3 of 7 studies with women after breast cancer could show an improvement of mild climacteric symptoms [59–61]. As a result of their low dosage and good tolerability, a first-class alternative treatment trial with specific phytopreparations such as, for example, *Cimicifuga racemosa* (black cohosh) can be recommended, even if they often show disappointing results when it comes to severe symptoms.

It is advisable to primarily use phytopreparations, for which breast cancer is not listed as a contraindication. There are different listings for the same groups of preparations, such as for *Cimicifuga racemosa* or red clover. To what extent these various differences are medically justified, or rather have a logistic-licensing technical basis is controversially discussed. At any rate, these differences should be observed on forensic grounds. Safety is however by no means guaranteed – propagated conclusions from in-house data pools, such as, for example, those produced regarding treatment with *cimicifuga* after breast cancer, cannot replace appropriately published controlled studies.

Opi Pramol and gabapentin are also relatively well tolerated and effective. Substances such as methyl dopa, clonidine or vitamin E show only very marginal, often absent effects, yet they can be tentatively used as well as Bellargal or Dong Quai, in order to motivate women towards a more effective medication. General measures to take to relieve menopausal symptoms are reduction of caffeine and nicotine intakes, appropriate clothing, avoidance of heat, exercise in fresh air, breathing and relaxation exercises and a balanced diet.

In the context of the controversial discussion on risks and benefits

Table 4. Treatment of menopausal symptoms after breast cancer – practical recommendations in rank order

1	herbal remedies	especially <i>cimicifuga racemosa</i>
2	serotonin reuptake inhibitors gabapentin	e.g. fluoxetine, venlafaxine, paroxetine
3	megestrol acetate (Medroxy- progesterone acetate)	
4	tibolone or HRT	especially transdermal estradiol, if necessary in combination with progestogens using preferably micronized progesterone, if possible in long cycles on the basis of vaginal ultrasound measurements

of HRT, numerous publications on alternatives for the treatment of climacteric complaints can be found. Aim of the present survey was to focus on facts for HRT after breast cancer and not to present exhaustively the facts on alternatives. Referring to this some comprehensive reviews are cited (e.g. [62–64]) (Tab. 4).

Practical Recommendations

As stated in the introduction, this overview aims to present the available facts on HRT after breast cancer and to assess the data for giving practical recommendations. The data, however, appear to be too weak to perform a risk assessment based on clinical studies. The existence of an enhanced recurrence risk can be derived from information on primary breast cancer risk as well as from biological plausibility. Therefore, in the case of climacteric complaints, the use of possible alternatives should be considered first, which should especially include forensic aspects due to the high-risk group. Thus, the preparations of groups 1–3 in Table 4 are not contraindicated in women after breast cancer (in case of *cimicifuga* only certain preparations). A further “hierarchy” results from the quality of the studies on climacteric complaints and the efficacy in relation to possible side effects and risks, respectively.

As mentioned before, as a result of low case numbers, no treatment principle is currently so confirmed that a risk-free therapy can be recommended. On the other hand, a nihilistic approach on the side of the doctor should be quashed on ethical grounds – every affected and severely suffering patient should be given a chance to co-decide on a possible treatment after an explanation appropriate to the individual.

It is advisable to begin with alternatives, which are not contraindicated. The authors’ opinion is that phyto-preparations such as *cimicifuga* or soya are currently preferable to SSRIs or SNRIs, contrary to other popular opinion. Other available data should be observed, especially possible interactions with tamoxifen and aromatase inhibitors. Corresponding to recommendations from the USA, a specific trial with megestrol acetate can be tried, as it is effective against menopausal symptoms and shows an antineoplastic effect. In the process, the patient’s metabolism, especially lipids should be checked; combination with a lipid-lowering agent such as a statin is indicated if necessary. Alternatively, tibolone can be considered, although the risk situation may not differ from the risk of using HRT, according to the studies LIBERATE and HABITS, respectively. For this reason, tibolone and HRT are listed in the same position in our “hierarchy” in Table 4.

If HRT is still necessary, treatment should be kept as short as possible and at a low dose. The lowest dose of hormone therapy can be given via a transdermal application (mono-, combi-patch, gel). In doing so, an unphysiological estrone level and abnormal, potentially genotoxic metabolites (which can increase the risk of breast cancer in certain situations, e.g. in smokers), can be avoided. It is advisable to supplement a progestogen, if required, as interval therapy, or even better, “on demand” after vaginal sonography results.

At this time, the question on the progestin choice cannot be answered. Based on the primary breast cancer risk, 2 observational studies are available showing different risks in the head-to-head comparison. In the French E3N-trial, the combination of estradiol with progesterone or dydrogesterone showed no increased risk

in contrast to various synthetic progestins after 7 years of treatment [65]. In the analysis of the well-known UK General Practice Research Data Base, the risk was enhanced only for oral administration, but not for transdermal application when using the same progestin, i.e. norethisterone acetate (NETA) [66].

However, to what extent an increase of risk can be avoided with progesterone or dydrogesterone or the particularly low-dose combination patch requires further studies. Recent specific assessments from the E3N cohort showed an increased risk at least for lobular cancer in terms of dydrogesterone and a tendency for progesterone after long-term treatment [67]. As we recently extensively reviewed, clinical as well as experimental data indicate a risk increase when applying an oral combination with the most widely used progestins, medroxyprogesterone acetate and NETA, for more than 5 years. However, it remains unclear whether this can be apportioned to HRT after breast cancer [67].

HRT should be limited to receptor-negative tumours when possible, and a relapse-free period of at least 2 years should be awaited. However, this cannot be recommended for study results, but rather for reasons of general caution and plausibility, respectively. The relevant patient consent should be documented in a legally valid manner. Although the currently available data (with the exception of one study) argue that HRT has no clinically relevant effect on the risk of relapse, the data is from studies with only a relatively small number of cases and which were subject to many flaws (bias), which so far could not be sufficiently accounted for, at least in observational studies. It is important to await the results of further randomised clinical studies and until then, to point out to women who are interested in HRT that the effect of HRT on the development of a relapse is unclear. This risk should only be accepted as an exception, after consideration of or trial of alternatives.

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