

Reprint from

International Journal of *clinical*
pharmacology
and therapeutics



Dustri-Verlag Dr. Karl Feistle
München-Deisenhofen

Isopropanolic black cohosh extract and recurrence-free survival after breast cancer

H.H. Henneicke-von Zepelin¹, H. Meden², K. Kostev³, D. Schröder-Bernhardi³,
U. Stammwitz¹ and H. Becher⁴

¹Schaper & Brümmer GmbH & Co. KG, Salzgitter, ²Diakoniekrankenhaus
Rotenburg/Wümme gGmbH, ³IMS Health GmbH & Co. OHG, Frankfurt am Main,
and ⁴Ruprecht-Karls-Universität, Abteilung Tropenhygiene und öffentliches
Gesundheitswesen, Heidelberg, Germany

Key words

black cohosh – breast
cancer – climacteric
symptoms – recur-
rence-free survival

Abstract. Objective: To investigate the influence of an isopropanolic Cimicifuga racemosa extract (iCR) on recurrence-free survival after breast cancer, including estrogen-dependent tumors. Methods: This pharmacoepidemiologic observational retrospective cohort study examined breast cancer patients treated at general, gynecological and internal facilities linked to a medical database in Germany. The main endpoint was disease-free survival following a diagnosis of breast cancer. The impact of treatment with iCR following diagnosis was analyzed by Cox-proportional hazards models, controlling for age and other confounders. Results: Of 18,861 patients, a total of 1,102 had received an iCR therapy. The mean overall observation time was 3.6 years. Results showed that iCR was not associated with an increase in the risk of recurrence but associated with prolonged disease-free survival. After 2 years following initial diagnosis, 14% of the control group had developed a recurrence, while the iCR group reached this proportion after 6.5 years. The primary Cox regression model controlling for age, tamoxifen use and other confounders demonstrated a protractive effect of iCR on the rate of recurrence (hazard ratio 0.83, 95% confidence interval 0.69 – 0.99). This effect remained consistent throughout all variations of the statistical model, including subgroup analyses. TNM status was unknown but did not bias the iCR treatment decision as investigated separately. Hence, it was assumed to be equally distributed between treatment groups. Correlation analyses showed good internal and external validity of the database. Conclusion: An increase in the risk of breast cancer recurrence for women having had iCR treatment, compared to women not treated with iCR is unlikely.

Introduction

The effectiveness of extracts of black cohosh (*Actaea racemosa*, formerly *Cimicifuga racemosa*) in the treatment of climacteric symptoms, in particular vasomotor symptoms, has been demonstrated over the years and in a number of recent clinical studies [Daiber 1983, Fischer et al. 2005, Lehmann-Willenbrock and Riedel 1988, Liske et al. 2002, Munoz and Pluchino 2003, Osmer et al. 2005, Pethö 1987, Stoll 1987, Uebelhack et al. 2006, Vorberg 1984, Warnecke 1985]. We refrained from reiterating this evidence. For women with a diagnosis of breast cancer, a traditional therapy for treating climacteric symptoms using hormone replacement therapy (HRT) is not indicated, due to the lack of conclusive evidence regarding tumor progression under the influence of estrogen [Holmberg and Anderson 2004, Rauthe et al. 2003]. In vitro [Bodinet and Freudenstein 2002, Burdette et al. 2003, Foster 1999, Nesselhut et al. 1993, Zierau et al. 2002] and in vivo [Einer-Jensen et al. 1996, Freudenstein et al. 2002, Liske et al. 2002, Nisslein and Freudenstein 2003] studies on the isopropanolic extract of the rootstock of *Cimicifuga racemosa* (iCR), the active ingredient in the products Remifemin and Remifemin plus (Schaper and Brümmer GmbH & Co. KG, Salzgitter, Germany), have shown no evidence of estrogenic effects on the breast or endometrium, or breast cancer promotion. Products containing this iCR have been suggested as a good first step for treating breast cancer patients who develop climacteric symptoms either spontaneously or as a result of adjuvant chemo- or hormone therapy [Rauthe et al. 2003].

Received
July 18, 2006;
accepted
November 4, 2006

Correspondence to
Prof. H. Becher
Ruprecht-Karls-
Universität, Abteilung
Tropenhygiene und
öffentliches
Gesundheitswesen, Im
Neuenheimer Feld 324,
69120 Heidelberg,
Germany
heiko.becher@
urz.uni-heidelberg.de

To date, systematic clinical safety data have been lacking regarding the use of iCR-containing products by patients with estrogen-dependent tumors. Using a retrospective cohort study design, in which investigators were blinded to subjects' iCR status, we accessed patient record data from one of the largest medical databases worldwide to test the hypothesis that treatment with either of the iCR-containing products following a diagnosis of breast cancer negatively influences disease-free survival, even among women with estrogen receptor-positive and/or progesterone receptor-positive tumors.

Methods

Anonymous data were obtained from the prospectively compiled IMS Disease Analyzer Mediplus database from the Institute for Medical Statistics (IMS Health) in Frankfurt, Germany [Dietlein and Schröder-Bernhardi 2002]. All women diagnosed with first primary breast cancer between July 1, 1992, and December 31, 2003, and treated at one of the 1,278 general or internal medicine or 233 gynecological practices in Germany providing information to the database were considered eligible for inclusion. Approval by an institutional review board was not required, as fully anonymous data were analyzed without impacting patient integrity.

The primary outcome measure of the study was disease-free survival following a diagnosis of breast cancer, in relation to the use of iCR-containing products (Remifemin® or Remifemin® plus). The diagnosis of a recurrence indicated the end of disease-free survival. Diagnoses of breast cancer and breast cancer recurrence were strictly defined. Both ICD-9 code C50 and text entries into the patient record were taken into account. The diagnosis of breast cancer was considered confirmed if at least two entries were made, at different points in time, of either ICD code C50, "breast carcinoma" or "breast cancer". In the case of a suspected diagnosis (i.e. ICD code N63.0 N64.9 or C50 plus a text entry of "exclusion of" or "suspicion of"), disease was considered confirmed if the C50 diagnosis was verified within 6 months. In the case of only a single entry of C50 or a single text entry of "breast carcinoma"

or "breast cancer", diagnosis was considered confirmed if this was followed either by a prescription for tamoxifen (ATC code L02BA01) or within 6 months by a breast cancer-indicated prescription for endocrine therapy (ATC code L02), radiation therapy, or cytostatic therapy. In the case of only a single entry of C50, diagnosis was considered confirmed if a text entry of "condition following" (C50) was included, or if a diagnosis of a recurrence was subsequently made.

Because the database contains no differential information regarding recurrence, strict criteria were used to establish a case of recurrence. In general, recurrence was defined as any local recurrence, any locoregional recurrence, any distant metastases, any contralateral breast cancer tumor and death attributed to breast cancer. Specifically, breast cancer recurrence was considered confirmed if the patient record contained either an appropriate text entry, an ICD code of C77, C78, C79, C80 following a diagnosis of breast cancer, a change in sides (contralateral tumor) in the text (i.e. first "left", then "right") combined with the diagnosis C50, an indication of a second breast tumor with other localization through a change in the ICD codes (i.e. C50.4 → C50.5), or the onset of a therapy with gonadotropin-releasing hormone (GnRH) analog (goserelin, Zoladex®, ATC-Code L02AE). The repeated entry of a C50 ICD code without an accompanying text comment was not considered a recurrence, just as the refinement of a diagnosis, such as C50.9 →, i.e. C50.5 was not sufficient for a diagnosis. Further insufficient criteria of recurrence included referrals, prescriptions for non-over-the-counter (OTC) analgesics, hospital admissions or change in the intervals of aftercare.

As of December 2003, we had identified a total of 47,795 patients in the database who met the initial inclusion criteria. Patients were subsequently excluded from the analysis if:

- their first diagnosis was determined to be a recurrent or a metastasized breast cancer (n = 2,079),
- they had a second primary tumor prior to or following their diagnosis (if the type of recurrence could not be determined) (n = 2,178),
- they had a follow-up time of less than 6 months following diagnosis (except if

Table 1. Select characteristics of the study sample by iCR exposure group.

n	iCR	No iCR
	1,102	17,759
Age at initial diagnosis (years) *		
≤ 40	5.4	6.3
41 – 45	10.9	5.9
46 – 50	16.7	8.5
51 – 55	22.2	10.7
56 – 60	19.6	13.6
61 – 65	12.9	14.5
66 – 70	7.0	12.8
71 – 75	3.6	11.1
> 75	1.6	16.6
Mean (years)	54.6	61.9
Standard deviation (years)	9.3	13.5
Mean follow-up time by age group (years)		
≤ 40	5.1	4.0
41 – 45	5.5	3.9
46 – 50	4.8	3.8
51 – 55	4.7	4.0
56 – 60	4.5	4.0
61 – 65	3.7	3.4
66 – 70	3.8	3.5
71 – 75	4.8	3.5
> 75	3.3	2.8
Overall	4.6	3.6
Mean number of entries per patient (excluding iCR and tamoxifen prescriptions)		
Total	36.5	20.9
Per year of follow-up	9.0	6.6
Tamoxifen therapy (yes) *	35.8	24.0

*Data are expressed as percentage (except for mean and standard deviation); iCR = isopropanolic extract of *Cimicifuga racemosa*.

- within this time period a recurrence was diagnosed) (n = 4,860),
- they had been prescribed *Cimicifuga* preparations other than iCR-containing products (n = 378), or
- their initial database entry (or suspected diagnosis) was not confirmed (n = 19,439).

Following exclusion for the above criteria, a final sample size of 18,861 patients remained for analysis.

For the analysis, patients were categorized into two main groups. The exposed group (cases) comprised those patients who received an iCR prescription at least once at any time between their breast cancer diagnosis and ei-

ther the diagnosis of a recurrence or the end of the study period. The non-exposed group (controls) comprised patients who were not prescribed iCR after their initial breast cancer diagnosis and before diagnosis of a recurrence or by the end of the study period.

The study was designed as a non-inferiority study. Thus, under the conventional null hypothesis, the risk of recurrence among cases is at least 25% greater than that of controls (hazard ratio, $HR \geq 1.25$). This is a generally accepted threshold for odds ratios in bioequivalence studies. A conventional type I error of 0.05 was considered acceptable.

The analyses were conducted using SAS version 8.1 (SAS Institute, Cary, NC, USA). Correlations were measured using Spearman's correlation coefficient. Descriptive analyses were conducted using Kaplan-Meier survival curves, estimated using the PROC LIFETEST procedure. Non-inferiority of the treatment was investigated by survival analyses using Cox-proportional hazards models adjusted for covariables (PROC PHREG).

Stratification by age was done using 5-year age groups. This method provides an appropriate adjustment for age for an arbitrary distribution of the confounding variable [Becher 2004]. Tamoxifen and iCR were included in the model as time-dependent binary variables [Hosmer and Lemshow 1999]. Number of prescriptions and referrals were either continuous or categorized into quartiles and included in the main model as potential confounding factors of the association between iCR use and breast cancer recurrence. To assess the validity of the database, further plausibility analyses were performed and comparisons were made between the literature and the characteristics of the study sample in terms of proportion of metastasized tumors at first diagnosis, age at diagnosis, recurrence rate and the ratio of patients treated with tamoxifen.

Results

A total of 18,861 women were included in the analysis. Of these, 1,102 were categorized as iCR users (cases) and 17,759 were categorized as non-iCR users (controls). Select characteristics of the study group by exposure status are presented in Table 1.

Table 2. Number of iCR prescriptions, by recurrence status.

	Recurrence	No recurrence	All
	n (%) [*]	n (%) [*]	n (%) [*]
0	3,145 (96.4)	14,614 (93.7)	17,759 (94.2)
1	21 (18.1)	317 (32.2)	338 (30.7)
2	21 (18.1)	160 (16.2)	181 (16.4)
3	10 (8.6)	99 (10.0)	109 (9.9)
4	9 (7.8)	65 (6.6)	74 (6.7)
5	9 (7.8)	64 (6.5)	73 (6.6)
6	7 (6.0)	28 (2.8)	35 (3.2)
7	2 (1.7)	36 (3.7)	38 (3.4)
8	2 (1.7)	29 (2.9)	31 (2.8)
9	5 (4.3)	22 (2.2)	27 (2.5)
10	2 (1.7)	18 (1.8)	20 (1.8)
11 – 15	6 (5.3)	65 (6.5)	71 (6.4)
16 – 20	9 (7.8)	28 (2.8)	37 (3.3)
21 – 25	4 (3.4)	14 (1.4)	18 (1.6)
26 – 30	3 (2.6)	16 (1.6)	19 (1.7)
31 – 35	1 (0.9)	6 (0.6)	7 (0.6)
36 – 40	2 (1.7)	6 (0.6)	8 (0.7)
41 – 50	3 (2.6)	6 (0.6)	9 (0.8)
> 50	0 (0.0)	7 (0.7)	7 (0.6)
Sum (with iCR)	116 (100.0)	986 (100.0)	1,102 (100.0)
Mean (with iCR)	5.2	6.0	5.9
Median (with iCR)	3.0	3.0	3.0
Sum (all patients)	3,261	15,600	18,861

^{*}Percentages for number of iCR prescriptions >0 based on subset of women with at least 1 iCR prescription; iCR = isopropanolic extract of *Cimicifuga racemosa*.

Patient characteristics

The overall mean age at diagnosis was 61.4 years (range 26 – 103, median 62), with 50% of patients between 52 and 72 years of age. Age at diagnosis differed between the two groups, with iCR-exposed patients on average 7.3 years younger than unexposed patients. The mean observation time from diagnosis to final physician visit or end of follow-up was 3.6 years (range 6 months to 11 years) and varied by exposure group. In all age groups, the iCR group had a longer follow-up time than did the control group. Depending on age group, this difference ranged from 0.3 – 1.6 years.

The number of entries in a subject's record, excluding prescriptions for iCR or tamoxifen, was higher for the iCR group than for the non-iCR group (36.5 vs. 20.9). This difference was partly due to the longer observation time, but cases also had a higher number of entries per year than did controls (9.0 and 6.6, respectively). We observed no significant correlations between age, duration of follow-up, number of entries and iCR status (data not shown).

The proportion of all patients receiving a tamoxifen prescription at some point during observation was 25%. In the iCR group, 394 women (35.8%) were treated with tamoxifen following their diagnosis. The sequence of

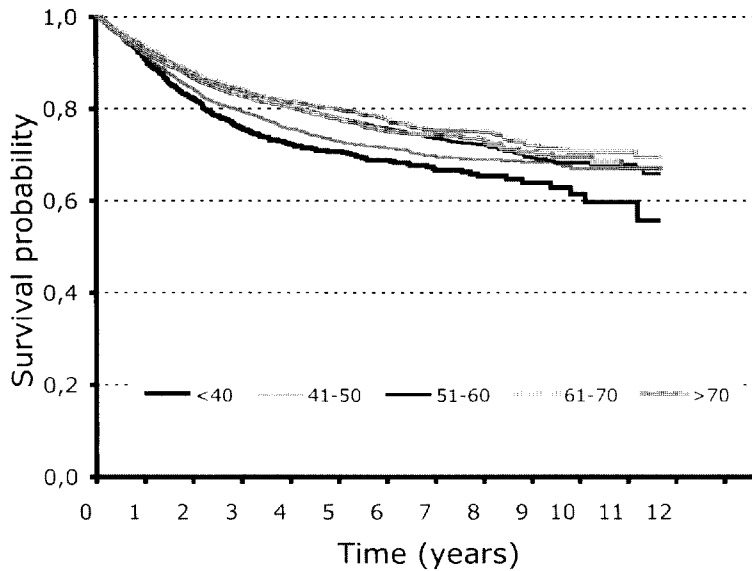


Figure 1. Recurrence-free survival in years, stratified by 10-year age-groups.

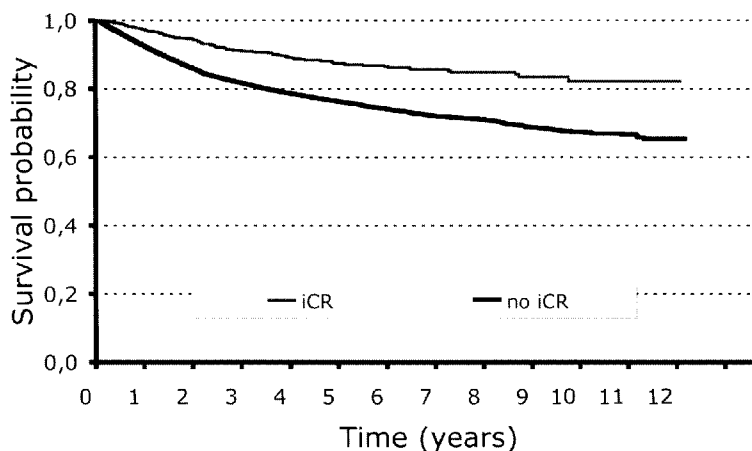


Figure 2. Recurrence-free survival in years, stratified by iCR exposure group; iCR = isopropanolic extract of *Cimicifuga racemosa*.

the prescriptions varied such that 178 patients received their tamoxifen prescription prior to their iCR prescription, 156 received their tamoxifen prescription following their iCR prescription, and 60 women received both prescriptions simultaneously. Among the controls, 24% received tamoxifen. A highly significant association was seen between iCR and tamoxifen, with tamoxifen patients 76% more likely to have been placed on iCR than their non-tamoxifen counterparts (OR 1.76; $p < 0.0001$) (data not shown). In the overall sample, the timing of first tamoxifen prescription showed two peaks: 38% of prescriptions were given within the first month following diagnosis and 39% over 6 months after diagnosis.

The number of iCR prescriptions showed a wide range, with nearly 1/2 of all iCR patients having 1 – 2 prescriptions, and 10% having 15 or more prescriptions (Table 2). In general, iCR applications tend to be divided into 1/2 prescriptions (1994: 53.3%, 1998: 58.6%, 2000: 47.4%) and 1/2 prescription-free self-medication [IMS VIP 2006]. Since one average iCR package at the recommended dosage amounts to a duration of therapy of approximately 50 days, each prescription in the database can be said to represent a mean exposure duration of 100 days (1 prescription plus 1 OTC). From the average number of iCR applications, we calculated an average duration of exposure of 590 days (median 300 days). For many tamoxifen patients, it can be assumed that at the first sign of side effect-based climacteric symptoms, an iCR prescription followed and that the patients themselves, after positive results, purchased refills without a prescription. An association between iCR and tamoxifen prescriptions was found both in the overall sample and within both recurrence and recurrence-free groups, with ORs of 2.12 (95% CI 1.87 – 2.32) and 1.67 (95% CI 1.46 – 1.91), respectively.

Risk of recurrence

The recurrence rate for the entire sample was 17.3% (3,261/18,861), with a yearly recurrence rate of 4.8%. In the iCR group, 113 (10.3%) patients developed a recurrence, as did 3,148 (17.7%) in the control group. The Kaplan-Meier estimates in Figure 1 show that, in accordance with the literature, recurrence-free survival is dependent on age, with the highest recurrence rates among the youngest patients.

Patients in the iCR group had a lower risk of recurrence, compared to patients in the control group. 2 years after initial diagnosis, 86% of all patients in the control group were recurrence-free, while this same proportion in the iCR group was not reached until the 6.5-year mark (Figure 2). This difference remained, even when we stratified the analysis by age group (Table 4). However, in the Kaplan-Meier estimates, the time of first iCR prescription after breast cancer diagnosis was not taken into account.

Table 3. Risk of recurrence for iCR use, adjusted for potential confounders.

Variables included in model	Adjusted hazard ratio for iCR*	95% CI	p value
iCR	0.75	0.63 – 0.89	0.001
iCR Tamoxifen	0.75	0.63 – 0.90	0.002
iCR Tamoxifen Entries per unit time	0.83 [†]	0.69 – 0.99	0.038
iCR Tamoxifen Prescriptions per unit time Referrals per unit time	0.83	0.69 – 0.99	0.040
iCR Tamoxifen Naturopathy	0.74	0.62 – 0.88	0.001

*All models adjusted for age; [†]Predefined main model; iCR = isopropanolic extract of *Cimicifuga racemosa*.

Table 4. Risk of recurrence for iCR use, by select subgroups.

Subgroup	n	Additional variables included in model*	Adjusted hazard ratio for iCR	95% CI	p value
Tamoxifen: yes	4,661		0.90	0.65 – 1.24	0.525
Tamoxifen: no	14,200		0.74	0.59 – 0.91	0.005
Age ≤ 55 years	6,191	Tamoxifen	0.82	0.65 – 1.04	0.105
Age > 55 years	12,670		0.66	0.51 – 0.87	0.003
Entries per year [†] ≤ 6.76	12,210	Tamoxifen	0.89	0.71 – 1.12	0.326
Entries per year > 6.76	6,651		0.87	0.65 – 1.15	0.322
Year of diagnosis < 2000	9,956	Tamoxifen	0.76	0.62 – 0.94	0.012
Year of diagnosis ≥ 2000	8,905	Entries per year >/< 6.76	0.77	0.55 – 1.07	0.118
Naturopathic prescriptions – yes	7,319	Tamoxifen	0.68	0.54 – 0.85	0.001
Naturopathic prescriptions – no	11,542		0.77	0.63 – 0.93	0.006

* All models stratified for age; [†]Dichotomized at median; iCR = isopropanolic extract of *Cimicifuga racemosa*.

A comparison of the iCR group and the control group by tamoxifen status revealed that iCR patients had a lower recurrence rate than did non-iCR patients, regardless of whether or not they had received tamoxifen (Figures 3, 4).

Table 3 shows the results from the primary model and its verifying models: a hazard rate ratio model estimating the association between iCR and risk of recurrence with and without individual covariables. 5-year age

groups were used as the stratification variable in each model. The model describing the effect of iCR on the risk of recurrence without other covariables was 0.75 (95% CI 0.63 to 0.89). Adding tamoxifen to the model had no effect on the hazard ratio (HR) of iCR, demonstrating that tamoxifen did not confound the effect of iCR on the risk of recurrence. A model including both iCR and tamoxifen and adjusting for prescriptions of naturopathic products resulted in an HR for iCR of 0.74

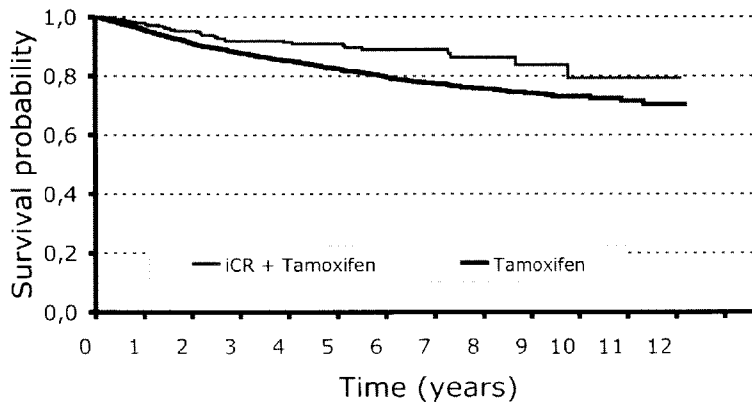


Figure 3. Recurrence-free survival in years, subgroup of tamoxifen users, stratified by iCR exposure group; iCR = isopropanolic extract of *Cimicifuga racemosa*.

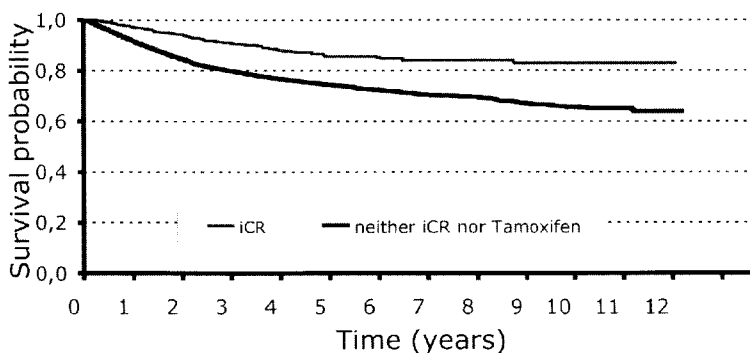


Figure 4. Recurrence-free survival in years, subgroup of tamoxifen non-users, stratified by iCR exposure group; iCR = isopropanolic extract of *Cimicifuga racemosa*.

(95% CI 0.62 – 0.88), indicating that treatment with naturopathic products played no role in the protractive effects of iCR on recurrences. A further model included both iCR and tamoxifen and was additionally adjusted for a continuous variable made up of total number of entries in a patient's record per year (referrals, prescriptions and diagnoses). Despite the fact that the number of record entries was identified as a potential confounding factor, its inclusion in the model reduced the protractive effect of iCR only slightly to HR 0.83 (95% CI 0.69 – 0.99). The main model of the analysis included iCR, tamoxifen, number of prescriptions per unit time (categorized into quartiles) and number of referrals per unit time (categorized into quartiles). Compared to the model in which number of entries was continuous, the effect in this model of iCR on the risk of recurrence

remained unchanged at HR 0.83 (95% CI 0.69 – 0.99). In addition, for the two variables of “number of prescriptions per year” and “number of referrals per year”, we observed a statistically significant inverse trend in association with recurrence risk. An unexpected finding in the primary model was the lack of an association between tamoxifen and the risk of recurrence (HR 1.00, 95% CI 0.91 – 1.1).

Subgroup analyses

In order to assess the variation within select subgroups of the effect of iCR on risk of recurrence, we conducted age-stratified subgroup analyses on the following binary variables: tamoxifen (yes/no), age group (bisected at 55 years), patient record entries per year (bisected at median 6.76), calendar year of diagnosis (bisected at 2000) and prescriptions of naturopathic products (yes/no). We examined age at diagnosis as both a prognostic factor in terms of disease-free survival and as a factor for treatment with the anti-estrogen tamoxifen. The number of entries per year could give an indication of the intensity of the therapy or care, although effects on the course of disease could not be excluded a priori. In terms of further naturopathic treatments, we considered the possibility that there could be patients who tried to improve their survival by adopting a naturopathic lifestyle. Year of diagnosis was chosen as a confounder, because entries in the database were spread out over a period of 12 years, in which time breast cancer therapy has undergone numerous changes through the establishment of new types of treatment and guidelines.

Point estimates for recurrence risk for iCR remained relatively constant, irrespective of subgroup, with HRs ranging from 0.66 – 0.90 (Table 4). None of the variables appeared to significantly modify the protractive effect of iCR on recurrence risk. The wide variance found in some of the models was due, in part, to small subgroup sample size, suggesting that the subgroup findings should be interpreted with caution.

We also examined the extent to which the level of iCR exposure influenced risk of recurrence, by creating an age-stratified model that included the number of prescriptions of either of the iCR-containing medical prod-

ucts as a time-dependent variable, categorized into 1, 2, 3–5, 6–8 and 9+, and adjusted for tamoxifen. No trend was seen for frequency of prescriptions on the risk of recurrence (data not shown).

Discussion

Previous studies have shown that breast cancer patients with a late recurrence have a longer survival time than those with an early recurrence [Bubb et al. 2003, Feige et al. 2001]. The major finding of our observational study is that isopropanolic black cohosh extract iCR found in Remifemin[®] or Remifemin[®] plus is not associated with an increased risk of breast cancer recurrence. Based on our analysis of 18,861 breast cancer patients, treatment with iCR was associated with prolonged disease-free survival and a 17% decrease in risk of recurrence. The effect remained consistent throughout all variations of statistical modeling, including subgroup analyses.

Because the database was not originally conceived to study recurrence, a number of variables with a relevant influence was not available for this analysis. These include receptor status and TNM status at the time of primary diagnosis. An association between these variables and iCR prescriptions would have meant a bias in our findings on the effect of iCR on recurrence. However, the fact that the point estimates observed for iCR were similar among both tamoxifen patients, who are most likely predominantly receptor-positive and non-tamoxifen patients, makes bias regarding receptor status unlikely.

The TNM status at first diagnosis and other factors play a decisive role in the individual prognosis of recurrence of each separate case. Regarding our analyses of groups instead of individuals, the lack of information on TNM status could introduce a bias only if iCR prescription was correlated with TNM status. However, we consider this unlikely for the following reasons:

- iCR is not marketed as anti-cancer agent but for relief of climacteric symptoms. The iCR-containing products have been known for 50 years to be suitable in any patient regardless the individual cancer history (e.g. no respective contraindica-

tion in the package leaflet or in the scientific product characteristics).

- There is no evidence that patients with an unfavorable breast cancer prognosis are prescribed Remifemin less or more often than patients with an early tumor stage at time of diagnosis. A study conducted in the Clinic for Tumor Biology at the University of Freiburg found no correlation between treatment decisions regarding iCR use and TNM classification, type of surgical intervention, chemotherapy (yes/no), radiotherapy (yes/no), age at cancer diagnosis and receptor status, but were associated with tamoxifen use [Fischer et al. 2005].

Of course, the lack of the individual prognostic data disadvantageously decreases the power to detect any difference between the groups. However, the power of our analysis was still sufficient to detect several hazard rate differences. The fact remains that the absence of TNM status data from our analysis precludes a more comprehensive anti-recurrence interpretation of our findings.

The frequency of iCR prescriptions in aromatase inhibitor users was insufficient for any statistical analysis.

This study set out to explore the hypothesis that use of iCR following first primary breast cancer diagnosis puts women at higher risk for recurrence. Our analysis was based on the IMS Disease Analyzer Mediplus database, one of the largest medical databases worldwide, currently containing data from as far back as the early 1990s on over 2.5 million German patients up to December 2003 (more than 11 million up to February 2006). The database extracts data from medical practices, checks for plausibility and validity, and links these to relevant additional information. Currently, over 90% of all contract doctors in Germany conduct their health insurance billing using clinical practice computing systems that feed into the database. Compared to other patient databases in Europe, Disease Analyzer is the only available database with direct linkages between diagnoses and corresponding therapies. The results deliver strong facts on everyday-life in medical practices. While the exposure to drugs is recorded over time in a valid manner, one consideration of our

analysis was the external validity of findings based on these data.

Our finding that 8.8% of patients had a primary metastatic breast carcinoma is in agreement with accounts in the literature, indicating 5 – 10% primary metastatic breast cancer [Basisdaten Mammakarzinom 2005, Feige et al. 2001, Sauer et al. 2003]. The age distribution of our patients was also representative: the Munich tumor registry reported that 10% of women were under 44 years of age in 1998 [Engel et al. 2001] and 25% and 75% of patients were under 50 years and under 70 years, respectively, in 1992/1993 [Basisdaten Mammakarzinom 2005]. Age at diagnosis in our study was similar to ages found in the cancer registries of both Munich (mean 61.2, median 60) and the Saarland (mean 63 years) [Krebs in Deutschland – Häufigkeiten und Trends 2004].

The yearly recurrence rate of 4.8% that we calculated from the database was in agreement with that of the 5 – 8% yearly progression rate found in reports in the literature [Sauer et al. 2003]. Our findings on the risk of recurrence decreasing with age were also in agreement with the literature [Survival Mammakarzinom 1997].

General data in the literature on the frequency of recurrence within age-groups are only available in relation to certain tumor stages or a defined therapy. However, there are data on frequency of progression, which theoretically should be only slightly higher than frequency of recurrence. The following 5-year follow-up data were reported from the German Cancer Organization: 40.3% progression for patients under 39 years of age, 28.6% for patients 40 – 49, 24.8% for patients 50 – 59, 25.1% for patients 60 – 69, and 18.9% progression for patients over 69 years of age [Deutsche Krebsgesellschaft e.V. 2005]. The agreement of these data with those of our database data indicates that our study findings on the frequency of recurrence can be considered valid. Overall, our data are consistent with the literature, proving that the database IMS Disease Analyzer produced representative answers to our main study question.

Because this study is observational, we generated a number of descriptive statistics and correlation calculations to test the internal validity of our results. The age difference be-

tween treatment groups is plausible, if we consider that women in younger age groups are more likely to experience climacteric symptoms than are older women. Hence, all our regression models did adjust for the confounder age by stratification. The fact that iCR was prescribed to 8.5% of all tamoxifen patients, but to only 5% of all non-tamoxifen patients suggests that iCR is prescribed specifically to combat the undesirable effects of adjuvant hormone therapy, in particular hot flushes.

Our findings on the difference in mean observation time by iCR group suggest a correlation with age, as older patients are, on average, more likely to die of any cause than their younger iCR group counterparts. This is evident in our data: patients in the iCR group were on average 7 years younger than the control group, and their observation time was on average approximately 1 year longer than that of the control group. It must also be noted that, in this simple comparison of observation times, time until first prescription was not taken into account and lead to an overestimation of the time difference. This was appropriately controlled for by Cox-regression with time-dependent covariables. The longer differences in observation time in age groups under 50 years are possibly linked to the higher recurrence rate of the control patients, when we consider that the recurrence diagnosis was also the end of observation in our analysis.

Our results on the timing of first tamoxifen prescription were plausible, since in general tamoxifen is prescribed either immediately following diagnosis or after a successful, usually not longer than 6-month cytostatic therapy. Thus, these database data are in agreement with the guidelines and consensus recommendations laid down for procedures following conclusion of a primary therapy [Jungmayr 2003]. A further reason for the cluster of tamoxifen first prescriptions within the first month following diagnosis is that in many cases, the date of first tamoxifen prescription was per definition the date of diagnosis in our analysis.

Considering that approximately 2/3 of all breast cancers are receptor-positive and, thus, potentially responsive to neoadjuvant hormone therapy, our finding of 25% tamoxifen use is lower than would be expected. These results are in agreement, however, with the findings of the Swedish HABITS study, in

which only 21% of patients were found to have received adjuvant tamoxifen [Holmberg and Anderson 2004]. Possible explanations for our low finding include: a) several patients received alternative forms of neoadjuvant therapy, including aromatase inhibitors, instead of tamoxifen, b) some women had ended their tamoxifen therapy by the time they entered the database, and c) incomplete data. Explanations a) and b) may have been due to the shorter therapies given in the 1990s, before the relatively recent development of the current optimal 5-year therapy [Wickerham 2002].

This study was not able to demonstrate an influence of tamoxifen on the recurrence rate in the study population. Although the finding that the likelihood of recurrence did not differ between the groups with and without tamoxifen may at first appear surprising, no conclusions can be drawn from this regarding the effectiveness of tamoxifen. Following the consensus recommendations which were in effect until 2003, the decision whether or not to treat with tamoxifen was dependent upon the tumor prognosis, whereby a fundamentally good recurrence prognosis was a reason to decide against a tamoxifen prescription. Tamoxifen was intended for use by mid- to high-risk postmenopausal patients [Feige et al. 2001]. It was not until 2003 that the consensus recommendations regarding adjuvant systemic therapy for breast cancer were changed to the effect that tamoxifen was recommended for use for all receptor-positive tumors [Kahlert et al. 2003]. Finally, our low proportion of tamoxifen users can be attributed to the fact that, even today, a significant portion of chronically ill patients, including breast cancer patients, are not being treated according to the latest scientific standards [Kreienberg 2006].

One strength of our study was the aspect of blinding, such that selection of database participants and identification of diagnoses were conducted without knowledge of iCR use, ensuring minimal selection bias. Our use of strict inclusion criteria for breast cancer diagnosis minimized possible misclassification bias and miscalculation of age at diagnosis. An additional strength was the duration of follow-up. Local recurrences occur more frequently in the first and second years following primary therapy. According to Bubb et al. [2003], a local recurrence develops, depend-

ing on adjuvant treatment but independent of primary therapy, in 5 – 10% of cases (5-year rate). In the present study, the mean overall follow-up time of 3.6 years was sufficient to make a statement regarding frequency of recurrences.

While we cannot exclude the possibility that some inaccuracies remain, the magnitude of these is likely to be small and non-differential. Similarly, the date of the diagnosis of recurrence also likely includes some inaccuracies. It is possible that the diagnosis will be entered at a later date, or the recurrence will be diagnosed at another health facility and either will not be recorded or will be recorded much later in the database. Again, this error is not expected to be differential by iCR use.

Our findings regarding the safety of iCR for women diagnosed with breast cancer are supported by clinical studies on iCR use among breast cancer patients [Briese et al. 2005, Fischer et al. 2005, Jacobsen et al. 2001, Munoz and Pluchino 2003] and in terms of breast density and breast epithelial proliferation [Hirschberg et al. 2005]. Of these, an open, prospective, randomized controlled trial among 136 tamoxifen patients demonstrated the benefits of a *Cimicifuga racemosa* therapy in combating the frequency and severity of hot flashes [Munoz and Pluchino 2003]. In that study, as in a prospective, randomized, placebo-controlled study with iCR [Hirschberg et al. 2005], no increased risk was observed. A recent drug observational study with iCR tablets on 50 patients being treated with tamoxifen confirmed the effectiveness and very good tolerance over a 6-month period of observation [Fischer et al. 2005].

A protective effect of iCR seems to be biologically plausible. Although the exact working mechanisms of iCR are not fully understood, preclinical studies indicate a selective estrogen-modulating effect (SERM) and possible central nervous dopamine properties [Boblitz et al. 2000]. Studies to date have demonstrated that the ingredients of black cohosh, while having estrogen receptor-binding properties, do not function identically to estrogen [Boblitz et al. 2000, Bodinet and Freudenstein 2002, Einer-Jensen et al. 1996, Foster 1999, Freudenstein et al. 2002, Hostanska et al. 2004, Liske et al. 2002, Nisslein and Freudenstein 2003, Viereck et al. 2005, Wuttke et al. 2006, Zierau et al.

2002]. Studies on other *Cimicifuga* extracts tend to deliver contradicting results. In the assessment of the question regarding drug safety, it is important to consider that differing extracts, such as methanolic, ethanolic or isopropanolic, may have varying effects and, therefore, exhibit varying risks [Loyda and Gruber 2000, Mueller et al. 2006].

In conclusion, our study provides some evidence that the isopropanolic black cohosh extract (iCR) does not increase the risk of breast cancer recurrence, even among patients with estrogen-dependent tumors.

Acknowledgment

Financial support for this study was sponsored by Schaper and Brümmer GmbH & Co. KG, Salzgitter, Germany.

References

- Basisdaten Mammakarzinom*. 1997, Deutsche Krebsgesellschaft e.V. Available at: <http://www.krebsinfo.de/ki/daten/mamma/bas1mamma.html>. Retrieved March 21, 2005.
- Basiszahlen zu M1- und progredienten Erkrankungen 1996 – 2001*. Deutsche Krebsgesellschaft e.V. Available at <http://www.krebsinfo.de/ki/epidaten/tab73.html>. Retrieved March 21st, 2005.
- Becher H. General principles of data analysis: continuous covariables in epidemiological studies. In: Ahrens W, Pigeot I (eds). *Handbook of epidemiology*. Berlin: Springer; 2004. pp. 595-624.
- Boblitz N, Liske E, Wüstenberg P. Black cohosh: efficacy, effect and safety of *Cimicifuga racemosa* in gynecology. *Dtsch Apoth Ztg*. 2000; 140: 107-114.
- Bodinet C, Freudenstein J. Influence of *Cimicifuga racemosa* on the proliferation of estrogen receptor-positive human breast cancer cells. *Breast Cancer Res Treat*. 2002; 76: 1-10.
- Briese V, Stammwitz U, Friede M, Stefenelli U, Henneicke-von Zepelin H-H. Wechseljahrestherapie ohne Hormone – Ergebnisse einer aktuellen Anwendungsbeobachtung. *J Menopause*. 2005; 12: 11-12.
- Bubb CF, Bauerfeind I, Baumeister RGH, Eiermann W, Engel J, Gabka C, Gauwerky J, Höss C, Lindner H, Untch M, Vehling-Kaiser U, Würschmidt F, Wuttge-Hannig A. Behandlung des lokalen und regionären Tumorrezidivs. *Manual Mammakarzinome*. München: Zuckschwerdt; 2003.
- Burdette JE, Liu J, Chen SN, Fabricant DS, Piersen CE, Barker EL, Pezzuto JM, Mesecar A, Van Breemen RB, Farnsworth NR, Bolton JL. Black cohosh acts as a mixed competitive ligand and partial agonist of the serotonin receptor. *J Agric Food Chem*. 2003; 51: 5661-5670.
- Daiber W. Klimakterische Beschwerden: ohne Hormone zum Erfolg! *Ärztl Prax*. 1983; 35: 1946-1947.
- Deutsche Krebsgesellschaft e.V. Survival (1) Mammakarzinom 1997. Available at: <http://www.krebsinfo.de/ki/daten/mamma/sur1mamma.html>. Retrieved March 1, 2005.
- Dietlein G, Schröder-Bernhardi D. Use of the mediplus patient database in healthcare research. *Int J Clin Pharmacol Ther*. 2002; 40: 130-133.
- Einer-Jensen N, Zhao J, Andersen KP, Kristoffersen K. *Cimicifuga* and *Melbrosia* lack oestrogenic effects in mice and rats. *Maturitas*. 1996; 25: 149-153.
- Engel J, Schubert-Fritschle G, Hölzel D. *Epidemiologie: Manual Mammakarzinome*. Tumorzentrum München: Zuckschwerdt; 2001.
- Feige A, Rempen A, Würfel W, Javny J, Caffier H. *Frauenheilkunde* (2nd ed). München: Urban und Fischer; 2001.
- Fischer J, Bartsch HH, Mumm A, Saller R, Stammwitz U, Rostock M. Prospektive Anwendungsbeobachtung mit einem *Cimicifuga racemosa* Extrakt (Remifemin) bei Mamma-Ca-Patientinnen mit klimakterischen Beschwerden unter Therapie mit Tamoxifen. *J Menopause*. 2005; 12: 12-13.
- Foster S. Black cohosh: *Cimicifuga racemosa* – a literature review. *HerbalGram*. 1999; 45: 35-50.
- Freudenstein J, Dasenbrock C, Nifflin T. Lack of promotion of estrogen-dependent mammary gland tumors in vivo by an isopropanolic *Cimicifuga racemosa* extract. *Cancer Res*. 2002; 62: 3448-3452.
- Hirschberg AL, Edlund M, Syvane G, Azavedo E, Skoog L von Schoultz B. An isopropanolic extract of black cohosh does not increase mammographic breast density or breast cell proliferation in postmenopausal women. *Menopause*. 2007; 14: 89-96.
- Holmberg L, Anderson H. HABITS (hormonal replacement therapy after breast cancer – is it safe?) – a randomised comparison: trial stopped. *Lancet*. 2004; 363: 453-455.
- Hosmer DW, Lemeshow S. *Applied survival analysis: regression modeling of time to event data*. New York: John Wiley and Sons; 1999.
- Hostanska K, Nisslein T, Freudenstein J, Reichling J, Saller R. *Cimicifuga racemosa* extract inhibits proliferation of estrogen receptor-positive and negative human breast carcinoma cell lines by induction of apoptosis. *Breast Cancer Res*. 2004; 84: 151-160.
- IMS VIP. (German Medical Index) Available at: <http://www.imshealth.de/sixcms/detail.php/313>. Retrieved February 14, 2006.
- Jacobsen JS, Troxel AB, Evans J, Klaus L, Vahdat L, Kinne D, Lo KMS, Moore A, Rosenman PJ, Kaufman EL, Neugut AI, Grann VR. Randomized trial of black cohosh for the treatment of hot flashes among women with a history of breast cancer. *J Clin Oncol*. 2001; 19: 2739-2745.
- Jungmayr P. Neue Leitlinien: St. Galler Konsensus-Konferenz 2003. *Dtsch Apoth Ztg*. 2003; 143: 5345-5347.
- Kahlert S, Bischoff J, von Bismarck F, Eiermann W, Funke I, Gutschow K, Harbeck N, Heinemann V, Janni W, Oberlechner E, Petrides P, Raab G, Salat C, Sattler D, Sauer H, Sommer H, Untch M, Zemzoum I. Adjuvante Hormon- und Chemotherapie. In: *Tumorzentrum München: Manual Mammakarzinome*. München: Zuckschwerdt; 2003.
- Krebs in Deutschland – Häufigkeiten und Trends 2004. Arbeitsgemeinschaft Bevölkerungsbezogener Krebs-

- register in Deutschland. Available at: http://www.rki.de/cln_011/nn_226978/DE/Content/GBE/DachdokKrebs/KrebsDownloads/kid_2004__templateId=raw,property=publicationFile.pdf/kid2004__. Retrieved October 18, 2005.
- Kreienberg R. Disease Management – Mammakarzinom – Qualitätskriterien aus Sicht der Deutschen Krebsgesellschaft. Available at http://www.krebsgesellschaft.de/download/dl_-_isto_-_artikel_disease_management_mammakarzinom.pdf. Retrieved February 14, 2006.
- Lehmann-Willenbrock E, Riedel HH. Klinische und endokrinologische Untersuchungen zur Therapie ovarieller Ausfallserscheinungen nach Hysterektomie unter Belassung der Adnexe. *Zentralbl Gynäkol.* 1988; 110: 611-618.
- Liske E, Hänggi W, Henneicke-von Zepelin HH, Boblitz N, Wüstenberg P, Rahlfs FW. Physiological investigation of a unique extract of black cohosh (*Cimicifuga racemosa* rhizoma): a 6-month clinical study demonstrates no systemic estrogenic effect. *J Womens Health Gend Based Med.* 2002; 11: 163-174.
- Loyda R, Gruber K. Safety and tolerability of different Hypericum extracts. *Phytomedicine.* 2000; 7: 20.
- Mueller SC, Majcher-Peszynska J, Uehleke B, Klammt S, Mundkowski RG, Miekisch W, Sievers H, Bauer S, Frank B, Kundt G, Drewelow B. The extent of induction of CYP3A by St. John's wort varies among products and is linked to hyperforin dose. *Eur J Clin Pharmacol.* 2006; 62: 29-36.
- Munoz GH, Pluchino S. Cimicifuga racemosa for the treatment of hot flushes in women surviving breast cancer. *Maturitas.* 2003; 44: 59-65.
- Nesselhut T, Schellhase C, Dietrich R, Kuhn W. Untersuchungen zur proliferativen Potenz von Phytopharmaka mit östrogenähnlicher Wirkung bei Mammakarzinomzellen. *Arch Gynecol Obstet.* 1993; 254: 817-818.
- Nisslein T, Freudenstein J. Synergistic effects of black cohosh and tamoxifen in an animal model of mammary carcinoma. *Maturitas.* 2003; 44 (Suppl): 128.
- Osmers R, Friede M, Liske E, Schnitker J, Freudenstein J, Henneicke-von Zepelin HH. Efficacy and safety of isopropanolic black cohosh extract for climacteric symptoms. *Obstet Gynecol.* 2005; 105: 1074-1083.
- Pethö A. Umstellung einer Hormonbehandlung auf ein pflanzliches Gynäkologikum möglich? *Ärztl Prax.* 1987; 39: 1551-1553.
- Rauhe G, de Waal JC, Engel J, Gutschow K, Höss C. Behandlungsmöglichkeiten von klimakterischen Beschwerden bei Patientinnen mit Mammakarzinom. *Internist Prax.* 2003; 43: 295-300.
- Sauer H, Artmann A, de Waal JC, Eiermann W, Gutschow K, Harbeck N, Heinemann V, Kessler M, Lutz L, Mahl G, Prechtel A, Rauhe G, Schmid L, Sittek H, Sommer H, Stieber P, Untch M, Wuttke-Hannig A. Nachsorge. Tumorzentrum München: Manual Mammakarzinome. München: Zuckschwerdt; 2003.
- Stoll W. Phytotherapeutikum beeinflusst atrophisches Vaginalepithel: Doppelblindversuch Cimicifuga vs. Östrogenpräparat. *Therapeutikon.* 1987; 1: 23-31.
- Uebelhack R, Blohmer JU, Graubaum H-J, Busch R, Gruenwald J, Wernecke K-D. Black cohosh and St. John's wort for climacteric complaints. *Obstet Gynecol.* 2006; 107: 247-255.
- Viereck V, Emons G, Wuttke W. Black cohosh: just another phytoestrogen? *Trends Endocrinol Metab.* 2005; 16: 199-248.
- Vorberg G. Therapie klimakterischer Beschwerden. *Z Allg Med.* 1984; 60: 626-629.
- Warnecke G. Beeinflussung klimakterischer Beschwerden durch ein Phytotherapeutikum. *Med Welt.* 1985; 36: 871-874.
- Wickerham L. Tamoxifen – an update on current data and where it can now be used. *Breast Cancer Res Treat.* 2002; 75: 7-12.
- Wuttke W, Gorkow C, Seidlova-Wuttke D. Effects of black cohosh (*Cimicifuga racemosa*) on bone turnover, vaginal mucosa, and various blood parameters in postmenopausal women: a double-blind, placebo-controlled, and conjugated estrogens-controlled study. *Menopause.* 2006; 13: 185-196.
- Zierau O, Bodinet C, Kolba S, Wulf M, Vollmer G. Antiestrogenic activities of *Cimicifuga racemosa* extracts. *J Steroid Biochem Mol Biol.* 2002; 80: 125-130.