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Contents

**ANALYSIS OF NUCLEAR RECEPTORS
CONSIDERING CELLULAR LOCALIZATION AND FOCALITY IN BREAST CANCER**

1. Introduction / *Einführung*

1.1 Epidemiology of breast cancer

In our ageing society, new cancer diagnoses are steadily increasing. Besides various environmental influences, the main causes are enhanced life expectancy and demographic change. According to the Robert Koch Institute, an increase of 20% in new cancer cases must be expected between 2010 and 2030 [45]. In the overall population, breast cancer, prostate cancer, lung cancer and colorectal cancer are the most common malignant tumors (Fig. 1). With an upward trend, breast cancer is the most frequent malignant tumor in women worldwide [26]. With 2.1 million incident cases in 2018 [8, 34], half a million deaths, and 14.9 million disability-adjusted life-years [22], breast cancer is still considered one of the utmost challenges for experts to regulate [39]. According to current statistics, one in eight women in Germany will develop breast cancer in the course of her life. This trend can be followed worldwide. Known risk factors for developing breast cancer include: female sex and age, obesity, prolonged endogenous estrogen exposure, long-term hormone replacement therapy in postmenopausal woman or nulliparity. In addition, a family history of breast cancer and a mutation in one of the breast cancer genes BRCA1 or BRCA2 also pose an increased risk [45].
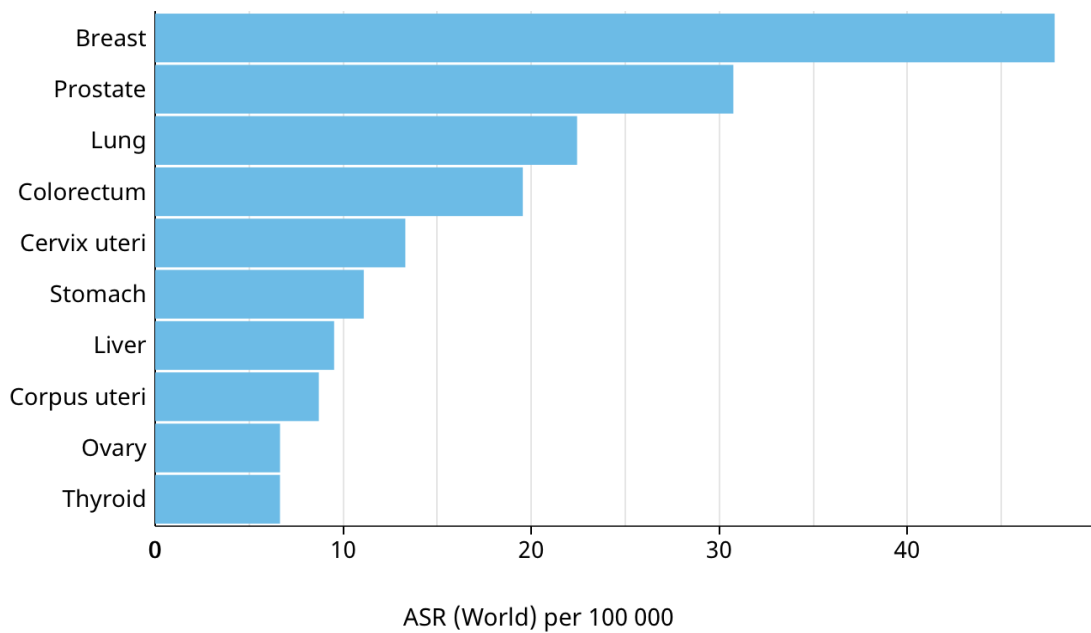
Figure 1: Estimated age-standardized incidence rates in 2020 worldwide (GLOBOCAN 2020 (IARC)[51])

Although much progress has been made in the field of diagnostics and therapy, the mortality rate of breast cancer is still high. In 2014, 17.670 patients succumbed to breast cancer in Germany alone [45]. Also due to the genetic component, breast cancer is not only a disease of old age. In contrast to many other malignancies, breast cancer also affects younger women more frequently. Almost three out of ten women are under 55 years old when first diagnosed [45]. Nevertheless, considerable progress has been achieved in the field of diagnostics and therapy. This has led to a decrease in mortality as observed over the last decades [13, 52] (Fig. 2). The trend can be explained by improved diagnostic possibilities, whereby tumors can be detected at an earlier and thus prognostically more favorable stage and further by systemic therapy approaches that have been enhanced, which could also contribute to a reduction in mortality [5, 27, 28].

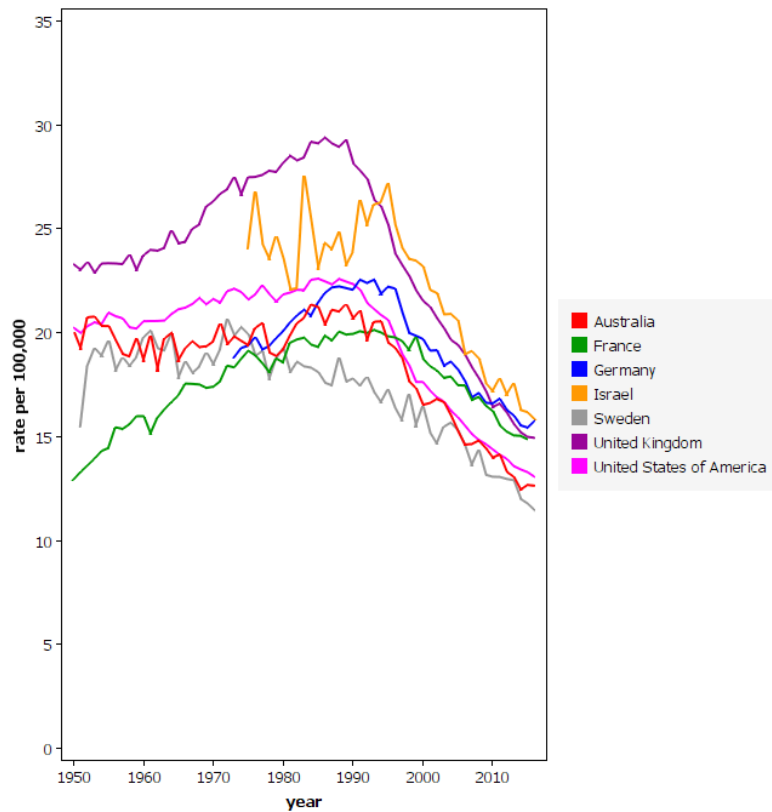Figure 2: Mortality from Breast cancer. The graph shows an age-standardized rate worldwide of all ages from 1950-2015 [52].

The epidemiological facts stated explain the high level of research interest in oncology on the subject of breast cancer. Aiming to reduce the morbidity and mortality of breast cancer, the development and investigation on new therapy strategies and drugs have increased tremendously over the past decades [27].

1.2. Breast cancer pathology and therapy

Treatment options for breast cancer have progressed tremendously over the past years. Therapy regimes in adjuvant, neoadjuvant, and metastatic settings advanced hugely reliant on clinical tumor subtypes and comprise chemotherapy, surgery, radiation, aromatase inhibitors, hormone-receptor modulators and quiet recently, immunotherapy [9, 19, 24, 27] . In addition to new therapy strategies, aiming to reduce the morbidity and mortality of breast cancer patients, research in recent decades has also progressed in the area of diagnostics and prognosis assessment. Aim of research and patient studies is to use existing therapies in a more targeted manner by analyzing different tumor characteristics and to further reduce undesirable side effects.

Research in the past decades was able to show that breast cancer is not one disease with different expressions, but is considered a cancer with different entities. According to the guideline from 2017, specific patient data and tumor characteristics should be collected to determine prognosis and prediction. These include age, menopausal status, pTNM, resection-margin, histological type, grading, lymphatic and blood vessel invasion, hormone receptor status and Her2neu status [1]. Research in the past decades has shown that a classification into hormone receptor positive and hormone receptor negative breast cancer is outdated. Further histological features including the Her2neu status has been implemented to allow a more decisive prognosis and new therapy options. The nowadays-established factors such as Ki-67 expression or uPA/PAI-1 can be used to further assess the prognosis. Furthermore, multigene assays have also been increasingly used in recent years with the aim to reduce chemotherapy use in clinically high-risk yet genomically low-risk breast cancer patients [27, 42].

The classification as recognized by the St. Gallen expert consensus distinguishes four prognostically relevant subtypes that take the histo-pathological markers into account: *Luminal A*, *Luminal B*, *Her2 expression* and *Basal-like* (Table 1) [23]. A diagnostic cascade allows to differentiate between low-risk and high-risk patients and the decision for the suitable therapy is ultimately based on the assessment of the course of the disease and the expected effect of the systemic therapy [16, 27]. According to the intrinsic breast cancer subtype, the broad implication for systemic treatment selection concurring to the St Gallen Expert Consensus 2013 is presented in Table 1 [23].

Intrinsic subtype	Clinico-pathologic definition	Type of therapy
Luminal A	*'Luminal A-like'* *all of:* ER and PR positive HER2 negative Ki-67 'low' Recurrence risk 'low' based on multi-gene-expression assay (if available)	Endocrine therapy is the most critical intervention and is often used alone.
Luminal B	*'Luminal B-like (HER2 negative)'* ER positive HER2 negative and at least one of: Ki-67 'high' PR 'negative or low' Recurrence risk 'high' based on multi-gene-expression assay (if available) *'Luminal B-like (HER2 positive)'* ER positive HER2 over-expressed or amplified Any Ki-67 Any PR	*'Luminal B-like (HER2 negative)'* Endocrine therapy for all patients, cytotoxic therapy for most. *'Luminal B-like (HER2 positive)'* Cytotoxics + anti-HER2 + endocrine therapy
Erb-B2 overexpression	*'HER2 positive (non-luminal)'* HER2 over-expressed or amplified ER and PR absent	Cytotoxics + anti-HER2
'Basal-like'	*'Triple negative (ductal)'* ER and PR absent HER2 negative	Cytotoxics

Figure 3. Definitions of intrinsic subtypes of breast cancer and their broad implications for systemic treatment selection according to the St Gallen Expert Consensus 2013 (modified according to Goldhirsch et al.)[23]

The realisation that breast cancer is composed of a large variety of biological subtypes has led to major advances in treatment. A multimodal therapeutic approach is nowadays pursued by combining local and systemic treatments, adapted to the risk profile of each patient, based on the above named individual factors. Endocrine therapies and systemic chemotherapies can be used in a more targeted way. Overall, a development towards individually adapted therapy concepts can thus increasingly be observed in the last decades.

1.3 Receptor expression in breast cancer

Malignancy and metastatic behavior as well as potential therapeutic options and the resulting prognosis in the biological subtypes of breast cancer (BC) are significantly related to the expression of various proteins and signalling cascades.

For distinguishing clinical tumor subtypes, BC focality is recognized as a significant prognostic factor [4, 40]. The focality is a meaningful factor affecting the progressive course of disease and has been described by multiple studies for multifocal and multicentric BC patients [7, 37, 50, 56]. Multifocality and/or multicentricity was found to be predictive of a worse prognosis through increased rates of distant metastasis, local relapse and shorter survival [50], prevalence of lymph node metastases [37], and higher mortality rates [7]. In contrast, unifocal BC is associated with a enhanced prognosis, including a better overall survival (OS) and disease free survival (DFS), in comparison to multifocal and/or multicentric BC with the same tumor size. However, the expression of nuclear receptors also in regards to the cellular localization have not been profoundly studied in association to breast cancer focality.

The estrogen (ER) and progesterone receptor (PR) are established "classical steroid hormone receptors" and are a key decision component in therapeutic approaches and anticipating prognosis for BC patients. Two major subgroups of nuclear receptors are known. The nuclear receptors of subgroup 1 include estrogen and progesterone receptors as well as androgen and mineralocorticoid receptors. The DFS of patients with hormone receptor-positive breast cancer can be significantly prolonged by the use of endocrine therapies [2, 3, 21] and the determination of the receptor status of ER and PR is part of the basic diagnostics in BC [1, 43].

In addition to the established markers, there are other receptors that are expressed by breast cancer cells and whose prognostic relevance has not yet been conclusively clarified [32]. These include the nuclear receptors: vitamin D3 receptor (VDR), retinoid X receptor (RXR) and thyroid hormone receptors (THRs), which are assigned to subgroup 2 of the nuclear receptors. These are all members of the nuclear hormone receptor superfamily [17] and are ligand-dependent transcription factors, which bind several lipophilic hormones and lipid metabolites [12]. The nuclear receptors are activated by binding with its ligands in order to form homodimers and heterodimers with many other members of the nuclear receptor superfamily [15]. After forming heterodimers [20], they

consequently translocate to the nucleus, bind to specific response elements upon promoters of specific genes, and thus act as transcription factors [35]. Various ligands bound to these receptors subsequently recruit different co-activators and accordingly regulate different genes and biological functions [35]. Personalized treatment options nowadays already involve drugs that target nuclear receptors [41].

Besides the recognized risk factors for BC, chronic inflammation has lately also been associated to tumor progression. The role of eicosanoids and their signaling pathway including their function in tumorigenesis have come into focus of recent research in various human cancer diseases. Multiple studies identified Cyclooxygenase-2 (COX-2) overexpression and increased PGE_2 levels in various malignant human cancers to be significantly associated with tumorigenesis, disease progression and a poor prognosis including metastatic behavior [10, 31, 44, 48]. When binding to its EP receptors (Prostaglandin E_2 receptor 1-4), PGE_2 is held responsible for stimulating tumor growth, angiogenesis, invasion, and conferring resistance to apoptosis [18, 25]. The EP receptor family indicates a unique function in BC tumorigenesis. Therapy options nowadays already involve the COX-2-pathway modulator Palbociclib for instance; a highly selective cyclin-dependent kinase 4/6 inhibitor (CDK4/6) that was able to validate a significant enhancement in the prognosis of metastatic BC [47].

The identification of the above-mentioned receptor expressions in human breast cancer specimens in regard to focality has not been studied. New insights could potentially be promising in regard to new cancer therapeutics and strategies for breast cancer patients.

2. Objective / *Zielsetzung*

The aim of this *Habilitation-project* is the analysis of nuclear receptors considering cellular localization and focality in breast cancer.

The intention is to assess the prognostic value of the nuclear receptors VDR, RXR alpha and THRs on the two different breast cancer focality entities: multifocal/multicentric versus unifocal. Furthermore, the prognostic impact of hormone- and EP3 receptor expression in relation to focality in breast cancer is investigated. The extent to which receptor expression correlates with known prognostic and predictive factors in relation to BC focality is subject of the analysis, anticipating a detailed description of the receptor-positive breast cancers and providing indications of their prognostic relevance.

For more detailed information on the methodology and the discussion of the individual studies, please refer to the corresponding original papers, which are cited at the relevant point and can be found in the overview on results section of this habilitation thesis.

3. Overview on results / *Eigene Ergebnisse*

3.1. EP3 is an independent prognostic marker only for unifocal breast cancer cases

EP3 is an independent prognostic marker only for unifocal breast cancer cases

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The prognostic relevance of EP3 in breast cancer relating to the cancers focality was the aim of this study.

In gynecological cancers, EP3 expression is described to either correlate positively with survival as defined for breast cancer [46], opposed to a negative association regarding outcome for ovarian [11] and cervical cancer patients [29]. The contradictory role of EP3 in gynecological cancers highlights the need to further research on the behavior of EP3 receptor expression in breast cancer. Consequently, the study examined the EP3 expression in unifocal versus multifocal sporadic breast cancer tissue samples and its impact on clinicopathological parameters, recurrence and survival.

The EP3 receptor was analyzed by immunohistochemistry in a series of 289 sporadic breast cancer patients treated at the Department of Gynecology and Obstetrics at the Ludwig-Maximillian's University in Munich. Retrospective statistical analysis on survival related events were carried out [56].

The study revealed a significant positive influence on survival for both focality entities, yet with interesting differences. Unifocal breast cancer tissue samples with high EP3 receptor expression exposed a significantly improved OS. Thus, EP3 was found to be a positive prognosticator for unifocal breast cancer and also displayed favorable outcomes regarding staging and grading. Furthermore, EP3 expression in unifocal breast cancer was even identified as an independent prognostic marker for OS, when adjusted for age, grading and staging. In contrast, EP3 receptor expression in multifocal/multicentric BC tissue samples merely showed a positive impact on OS five years after initial diagnosis and proved to be a dependent prognosticator.

The results obtained encourage a discussion on markers linked to inflammation and the different effects on prognosis and clinicopathological parameters for each focality type. The study aimed to serve as a scientific base for future specific EP3 targeted BC therapy adopted to the focality.

3.2. Hormone receptor expression in multicentric/ multifocal versus unifocal breast cancer: especially the VDR determines the outcome related to focality

The study evaluates the prognostic impact of ER, PR and VDR in relation to breast cancer focality: multifocal versus unifocal.

To this point, several studies highlight the benefit of increased VDR as well as hormone receptor-positive (ER and PR positive) BC expression, yet data under the aspect of the BC focality type are still lacking. VDR expression is described to be inversely associated with elevated BC cancer incidences, disease progression and poorer prognosis [14, 38]. Regarding ER and PR, hormone receptor-positive BC is to this date held accountable for the majority of the disease related deaths and is thus of major interest in BC research [33]. The nuclear receptor expressions were analyzed in a retrospective analysis in a series of 320 breast cancer patients treated at the Department of Gynecology and Obstetrics at the Ludwig-Maximillian's University in Munich. All three by immunohistochemistry analyzed nuclear receptors presented a significantly positive influence on survival, however, only for unifocal BC [55]. Triple negative BC cases were associated with a worse prognosis for patients with unifocal BC. In patients with multifocal BC, the hormone receptor expression (ER and/or PR) did not verify a significant association to prognostic markers. Unifocal BC cases are significantly and positively correlated with increased VDR expression regarding the Grading and TNM staging. In contrast, multifocal BC patients revealed a worse DSF and were more often staged pM≥1, when expressing the VDR. The

findings demonstrate a remarkably paradox role of VDR expression regarding BC prognosis. The outcomes are strengthened by the fact that the ER in unifocal breast cancer and the VDR in multifocal breast cancer were identified as independent prognostic markers for OS, when adjusted for age, grading and staging.

The study investigated the behavior of the nuclear hormone receptors in BC and the different effects on each focality type. Adopted vitamin D supplementation in breast cancer patients depending on focality is center of discussion.

3.3.   The Prognostic Impact of Retinoid X Receptor alpha and Thyroid Hormone Receptor alpha in Unifocal vs. Multifocal/Multicentric Breast Cancer

The prognostic value of RXR alpha and THRs expression, on the two different breast cancer entities: multifocal/multicentric versus unifocal was analyzed [57]. RXR alpha is recognized to have tumor suppressor properties and inhibit cell proliferation. Previous studies suggest that RXR alpha positivity may predict favorable prognosis in breast cancer and comprise anti-cancer cell activity [6, 30, 53]. Furthermore, evidence implies a correlation between breast cancer and thyroid disorders. Patients with thyroid dysfunctions show increased breast cancer incidences in contrast to healthy women [36, 49].

To determine the role of RXR alpha and THRs in regard to BC focality, a retrospective statistical analysis was carried out on survival related events in a series of 319 sporadic BC patients treated at the Department of Gynecology and Obstetrics at the Ludwig-Maximillian's University in Munich. RXR alpha and THRs (including its isoforms)

expression were analyzed by immunohistochemistry and exposed a significant correlation for both BC entities regarding survival analysis.

Interestingly and despite previous reports supporting an anti-tumorigenic effect of increased RXR alpha expression, patients with multifocal/multicentric BC exposed a significant worse DFS when expressing RXR alpha. Patients with unifocal BC presented a significant worse DFS when expressing THRα1, whereas a significant positive association between THRα2 expression and improved DFS in multifocal/multicentric BC was revealed.

The outcomes suggest a critical review of possible molecular therapies targeting nuclear receptors in BC treatment and strengthen the need to further examine the role of the nuclear receptor family.

These findings consequently encouraged to further analyze the RXR alpha regarding its subcellular localization; cytoplasmic versus nucleus RXR alpha expression, to allow a more profound understanding for the remarkably incongruous role.

3.4. Cytoplasmic localization of RXR Alpha Determines Outcome in Breast Cancer

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Our previous study has identified the RXR alpha expression as a risk factor with a significant worse DFS in patients with multifocal or multicentric BC [57]. Because of the alleged contradictory behavior of RXR alpha for breast cancer prognosis, further investigations are of major interest to determine the exact role of RXR alpha in BC. To allow a profound understanding, the aim of this study was to identify the subcellular localization of RXR alpha in relation to prognosis determining aspects in breast cancer [54].

In 319 BC tissue samples, the expression of RXR alpha was evaluated by immunohistochemistry and prognosis determining aspects were calculated by uni- and multivariate analysis [54].

Interestingly, a trend association with nuclear RXR alpha expression regarding an improved OS was observed. In contrast, significantly poorer outcome in both OS and DFS in patients with cytoplasmic RXR alpha expression was detected. Cytoplasmic RXR alpha was even found to be an independent marker for DFS, when adjusted to clinicopathological parameters. Nuclear RXRα expression, on the other hand, was positively associated with lower TNM-staging, whereas cytoplasmic RXRα expression was positively associated with a higher histopathological tumor grading. In summary, nuclear RXR alpha expression seems to be a protective factor in BC whereas cytoplasmic RXR alpha is correlated with a more aggressive course of the disease.

The study emphasizes the fact that the localization of the subcellular localization of RXR alpha plays a significant role in carcinogenesis and prognosis of BC. Identification of high-risk BC subgroups is subject of this study in wise prospect of potential individualized targeted BC therapies [54].

4. Summary and future outlook / *Zusammenfassung und Ausblick*

The aim of this cumulative *Habilitation-thesis* was the analysis of nuclear receptors considering cellular localization and focality in breast cancer, in order to identify molecular biological target structures that can be considered as new diagnostic or therapeutic starting points.

The treatment of breast cancer has already emerged to an exceptional multimodal therapy concept over the past decades. Currently, various prognostically relevant features have been linked to the presently used four histo-pathological subtypes (*Luminal A, Luminal B, Her2, Basal-like*), which represent the different entities of breast cancer. Highly individualized therapy concepts are developed on the basis of these different and increasingly diverse biomarkers as well as gene mutation analyses. The ideal treatment considered is finally a balance struck between adequate oncological safety and therapy-associated toxicities and side effects. Breast cancer is no longer considered as one solitary disease, but rather as one that is composed of a large variety of biological entities. The knowledge about various subtypes differing in their tumor biology and thus also in their prognosis has finally encouraged a development towards this "tailor-made" therapy concept. These individually, to the patients' tumor characteristics, adapted strategies have also consequently led to a decrease in mortality. Accordingly, personalized treatment approaches can be regarded as the key to further reduce morbidity and mortality in breast cancer. Particularly, in triple negative breast cancer, which is characterized by worse OS, DFS and increased metastatic potential compared with other major breast cancer subtypes, the identification of reliable predictive biomarkers is indispensable to find new therapeutic regimes.

To sum up, essential for further expertise and therapy development is the identification of new therapeutic targets. The biomarkers investigated in this thesis were selected on the ground of existing promising results in signaling cascades and their observed interaction with biomarkers of proven prognostic relevance.

Receptor expression of patients with sporadic BC treated at the Department of Gynecology and Obstetrics, Ludwig-Maximillian's University in Munich, were verified by

immunohistochemistry and analyzed by IRS and exposed a significant association for both BC entities in regard to survival. The results confirm an important role of the receptor expression at the cellular level in the pathogenesis of BC and suggest a prognostic relevance.

Regarding the results of EP3 expression in BC, the receptor was found to be a positive prognosticator for OS in unifocal breast cancer and also displayed favorable outcomes regarding staging and grading. EP3 expression was even identified as an independent prognostic marker for OS in unifocal BC. The outcomes obtained encourage a discussion on markers linked to inflammation and the different effects on prognosis and clinicopathological parameters for each focality type. The contradictory role of EP3 in gynecological cancers should further be assessed.

Considering the outcomes of the nuclear receptor expressions in breast cancer, VDR, RXR alpha and THRs each revealed a prognostic relevance in relation to the different breast cancer focality entities: multifocal/multicentric versus unifocal. Patients with unifocal breast cancer presented a significant worse DFS when expressing THRα1, whereas a significant positive association between THRα2 expression and improved DFS in multifocal/multicentric breast cancer was shown.

Concurrent to previous findings about the protective role of VDR, our results revealed that unifocal BC cases are significantly and positively associated with increased VDR expression regarding the Grading and TNM staging. In contrast and despite former reports supporting an anti-tumorigenic effect of increased VDR and RXR alpha expression, patients with multifocal/multicentric breast cancer exposed a significant worse DFS when expressing VDR and RXR alpha. Increased VDR expression in multifocal/multicentric breast cancer was even identified as an independent prognostic marker for OS and these patients were furthermore more often staged pM≥1. The findings demonstrate a remarkably paradox role of VDR and RXR alpha expression regarding breast cancer prognosis for multifocal/multicentric patients. In terms of VDR, a vitamin-D supplementation for the prophylaxis of cancer therapy side effects is commonly used nowadays and consequently an adopted vitamin-D supplementation in breast cancer patients depending on focality should thus further be assessed.

These findings consequently encouraged to further analyze the RXR alpha in regard to its subcellular localization: cytoplasmic versus nuclear RXR alpha expression, to allow a more profound understanding for the remarkably incongruous role. Nuclear RXR alpha

expression revealed to be a protective factor in breast cancer whereas cytoplasmic RXR alpha is associated with a more aggressive course of the disease. A trend association with nuclear RXR alpha expression regarding an improved OS was observed. In contrast, significantly poorer outcome in both OS and DFS in patients with cytoplasmic RXR alpha expression was detected and was found to be an independent marker in cytoplasmic RXR alpha expression for DFS.

Overall, the investigated receptors, especially regarding BC focality, demonstrate a significant association to prognostic and predictive markers. Each individual receptor property suggests a foundation to potentially function as new prognostic and predictive factors. To conclude, nuclear receptors in breast cancer and possible targeted treatments should become subject of future research by verifying the results of this project in a larger breast cancer collective. Furthermore, the prognostic relevance regarding the complex cellular processes and the various histo-pathological subtypes should be taken into account. Specifically, the results obtained confirm the need of further research on the subcellular expression of members of the nuclear hormone receptor superfamily, which is currently subject of investigation in our study group. To this point, we achieved gripping results that will hopefully be relevant for further detailed studies.

The aim of this preclinical study is to expectantly build a foundation upon which future personalized treatments for breast cancer can be built.

5. Abbreviations / *Abkürzungsverzeichnis*

BC	Breast cancer
BRCA	Breast cancer antigen
CDK4/6	Cyclin-dependent kinase 4/6 inhibitor
COX	Cyclooxygenase
DFS	Disease free survival
DNA	Deoxyribonucleic acid
EP3	E2-Receptor 3
ER	Estrogen receptor
G 1/2/3	Grading 1/2/3
HER2neu	Human Epidermal Growth Factor Receptor 2
HRE	Hormone responsive element
IRS	Immmunoreactive score
NR	Nuclear receptor
OS	Overall survival
PAI-1	Plasminogen activator inhibitor-1
PR	Progesterone receptor
RAR	Retinoic acid receptor
RXR	Retinoid X receptor
RXRα	Retinoid X receptor alpha
TC	Total collective
THR	Thyroid hormone receptor
THRα	Thyroid hormone receptor alpha
(p)TNM-Classification	(pathological) Tumor-Node-Metastasis Classification
uPA	Urokinase plasminogen activator
VDR	Vitamin D3-receptor
WHO	World Health Organization

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55.   Zati Zehni, A.; Jacob, S. N.; Mumm, J. N.; Heidegger, H. H.; Ditsch, N.; Mahner, S.; Jeschke, U.; Vilsmaier, T., Hormone Receptor Expression in Multicentric/Multifocal versus Unifocal Breast Cancer: Especially the VDR Determines the Outcome Related to Focality. *Int J Mol Sci* **2019,** 20, (22).

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7. Complete list of publications / *Vollständiges Schriftenverzeichnis*

Originalarbeiten als Erst- oder Letztautor

Cytoplasmic Localization of RXRα Determines Outcome in Breast Cancer

Alaleh Zati zehni, Falk Batz, Vincent Cavaillès, Sophie Sixou, Till Kaltofen, Simon Keckstein, Helene Hildegard Heidegger, Nina Ditsch, Sven Mahner, Udo Jeschke, **Theresa Vilsmaier**

Cancers 07/2021
IF: 6,64

The decidual expression of Interleukin-7 is upregulated in early pregnancy loss

Theresa Vilsmaier, Niklas Amann, Sanja Löb, Elisa Schmoekel, Christina Kuhn**,** Alaleh Zati zehni, Sarah Meister, Susanne Beyer, Theresa M. Kolben, Johanna Becker, Jan-Niclas Mumm, Sven Mahner, Udo Jeschke, Thomas Kolben

American Journal of Reproductive Immunology 04/2021
IF: 2,74

How The COVID-19 Pandemic Effects Sexual Behavior Of Hetero-, Homo-, and Bisexual Males in Germany

Jan-Niclas Mumm*, **Theresa Vilsmaier***, Julius Schütz, Severin Rodler, Alaleh Zati zehni, Ricarda M. Bauer, Michael Staehler, Christian Stief, Falk Batz
*The authors both contributed equally to this work (Co-First)

Sexual Medicine, 04/2021
IF: 2,49

Interleukin-1 beta is significantly upregulated in the decidua of spontaneous and recurrent miscarriage placentas

Sanja Löb, Niklas Amann, Christina Kuhn, Elisa Schmoeckel, Achim Wöckel, Alaleh Zati zehni, Till Kaltofen, Simon Keckstein, Jan-Niclas Mumm, Sarah Meister, Thomas Kolben, Sven Mahner, Udo Jeschke, **Theresa Vilsmaier**

International Journal of Reproductive Immunology 01/2021
IF: 4,05

The Prognostic Impact of Retinoid X Receptor and Thyroid Hormone Receptor alpha in Unifocal vs. Multifocal/Multicentric Breast Cancer

Alaleh Zati zehni, Falk Batz, Aurelia Vattai, Till Kaltofen, Svenja Schrader, Sven-Niclas Jacob, Jan-Niclas Mumm, Helene Hildegard Heidegger, Nina Ditsch, Sven Mahner, Udo Jeschke, **Theresa Vilsmaier**

International Journal of Molecular Sciences 01/2021
IF: 5,92

Pregnancy Zone Protein (PZP) is significantly upregulated in the decidua of recurrent miscarriage placentas and negatively correlated to Glycodelin A (GdA)

Sanja Löb, Aurelia Vattai, Christina Kuhn, Elisa Schmoeckel, Sven Mahner, Achim Wöckel, Thomas Kolben, Christiane Keil, Udo Jeschke, **Theresa Vilsmaier**

International Journal of Reproductive Immunology 12/2020
IF: 4,05

Interleukin 15 and Eotaxin correlate with the outcome of breast cancer patients vice versa independent of CTC status

Theresa Vilsmaier, Helene Hildegard Heidegger, Lennart Schröder, Elisabeth Trapp, Alaleh Zati zehni, Brigitte Rack, Wolfgang Janni, Sven Mahner, Tobias Weissenbacher, Udo Jeschke, Jan-Niclas Mumm, SUCCESS Study Group

Arch Gynaecol Obstet, 09/2020
IF: 2,36

Splicesome protein Eftud2 is upregulated in the trophoblast of spontaneous miscarriage and hydatidiform mole pregnancy placentas

Sanja Löb, Christoph Scholz, Aurelia Vattai, Simone Hofmann, Christina Kuhn, Elisa Schmoeckel, Sven Mahner, Achim Wöckel, Thomas Kolben, Julia Szekeres-Bartho, Udo Jeschke, **Theresa Vilsmaier**

International Journal of Reproductive Immunology 08/2020
IF: 4,05

EP3 is an independent prognostic marker only for unifocal breast cancer cases

Alaleh Zati zehni, Udo Jeschke, Anna Hester, Thomas Kolben, Nina Ditsch, Sven-Niclas Jacob, Jan-Niclas Mumm, Helene Hildegard Heidegger, Sven Mahner, **Theresa Vilsmaier**

International Journal of Molecular Sciences, 06/2020
IF: 5,92

Hormone Receptor Expression in Multicentric/Multifocal versus Unifocal Breast Cancer: Especially the VDR Determines the Outcome Related to Focality

Zati zehni A, Jacob SN, Mumm JN, Heidegger HH, Ditsch N, Mahner S, Jeschke U, **Vilsmaier T,**

International Journal of Molecular Sciences, 11/2019
IF: 4,56

Publikationen als Erstautor zum Erwerb der eigenen Dissertation und werden für die Publikationsleistung im Habilitationsverfahren nicht gewertet

Influence of circulating tumor cells on production of IL-1α, IL-1ß and IL-12 in sera of patients with the primary diagnosis of breast cancer before treatment

Theresa Vilsmaier, Brigitte Rack, Alexander König, Klaus Friese, Wolfgang Janni, Udo Jeschke, Tobias Weissenbacher, SUCCESS Study Group

Anticancer Research, 10/2016
IF: 2,06

Angiogenic cytokines and their influence on circulating tumour cells in sera of patients with the primary diagnosis of breast cancer before treatment

Theresa Vilsmaier, Brigitte Rack, Wolfgang Janni, Udo Jeschke, Tobias Weissenbacher, SUCCESS Study Group

BMC Cancer, 07/2016
IF: 3,30

Originalarbeiten als Koautor

Dynamics of urinary and respiratory shedding of Severe acute respiratory syndrome virus 2 (SARS-CoV-2) RNA excludes urine as a relevant source of viral transimission

Jan-Niclas Mumm, Stephan Ledderose, Andreas Ostermann, Martina Rudelius, Johannes C Hellmuth, Max Münchhoff, Dieter Munker, Clemens Scherer, Yannic Volz, Benedikt Ebner, Clemens Giessen-Jung, Christopher Lampert, **Theresa Vilsmaier**, Stephanie Schneider, Madeleine Gapp, Katrin Milger-Kneidinger, Jürgen Behr, Michael von Bergwelt-Baildon, Oliver T Keppler, Christian Stief, Giuseppe Magistro, Michael Staehler, Severin Rodler

Infection 10/2021
IF: 3,55

The role of Interleukin-18 in recurrent early pregnancy loss

Sanja Löb, Beate Ochmann, Zhi Ma, **Theresa Vilsmaier**, Christina Kuhn, Elisa Schmoeckel, Saskia-Laureen Herbert, Thomas Kolben, Achim Wöckel, Sven Mahner, Udo Jeschke,

International Journal of Reproductive Immunology 10/2021
IF: 4,05

Identification of a Novel Tumor Microenvironment Prognostic Signitaure for Advanced-Stage Serous Ovarian Cancer

Mingjun Zheng, Junyu Long, Anca Chelariu-Raicu, Heather Mullikin, **Theresa Vilsmaier**, Aurelia Vattai, Helene Hildegard Heidegger, Falk Batz, Simon Keckstein, Udo Jeschke, Fabian Trillsch, Sven Mahner, Till Kaltofen

Cancers, 07/2021
IF: 6,64

Age at surgery is not a prognostic factor for the AdVance-XP male sling efficacy: a post-hoc analysis of a prospective seven-year multi centric study

Jan-Niclas Mumm, Benazir Abrarova, Julius Schütz, Benedikt Klehr, Severin Rodler, **Theresa Vilsmaier**, Christian Gozzi, Peter Rehder, Florian May, Roland Homberg, Peter Gebhartl, Christian G. Stief, Alexander Buchner, Ricarda M. Bauer

Neurourology and Urodynamics, 05/2021
IF: 2,04

Well-being during COVID-19 pandemic: A comparison of individuals with minoritized sexual and gender identities and cis-heterosexual individuals

Sonia Lech, Eva Lermer, Mirjam Fischer, Maximilian Berger, **Theresa Vilsmaier**, Till Kaltofen, Simon Keckstein, Sven Mahner, Joachim Behr, Christian J. Thaler, Falk Batz

PLOS ONE, 05/2021
IF: 3,24

Choosing a Specialist: An Explanatory Study of Factors Influencing Patients in Choosing a Urologist

Alexander Tamalunas, Alexander Buchner, Martin Hennenberg, Leo Federico Stadelmeier, Henrik Höhn, **Theresa Vilsmaier**, Maja-Lena Mumm, Thomas Kolben, Christian G. Stief, Michael Staehler, Jan-Niclas Mumm

Urologia Internationalis, 04/2021
IF: 1,69

Listening to music during outpatient cystoscopy reduces pain and anxiety and increases satisfaction: results from a prospective randomized study

Jan-Niclas Mumm, Lennert Eismann, Severin Rodler, **Theresa Vilsmaier**, Alaleh Zati zehni, Maria Apfelbeck, Pauolo L. Pfitzinger, Yannik Volz, Michael Chaloupka, Ricarda M. Bauer, Christian Stief, Michael Staehler

Urologia Internationalis, 04/2021
IF: 1,69

Nuclear Receptor corepressor (NCoR) is a positive prognosticator for cervical cancer

Beilner D Kuhn C, Kost BP, **Vilsmaier T**, Vattai A, Kaltofen T, Mahner S, Schmoeckel E, Dannecker C, Jückstock J, Mayr D, Jeschke U, Heidegger HH

Archives of Gynecology and Obstetrics, 04/2021
IF: 2,28

EP4 as a Negative Prognostic Factor in Patients with Vulvar Cancer

Anna Buchholz, Aurelia Vattai, Sophie Fürst, **Theresa Vilsmaier**, Christina Kuhn, Elisa Schmoeckel, Doris Mayr, Christian Dannecker, Sven Mahner, Udo Jeschke, and Helene H. Heidegger

Cancers, 03/2021
IF: 6,64

Immunogenomic Identification for Predicting the Prognosis of Cervical Cancer Patients

Qun Wang, Aurelia Vattai, **Theresa Vilsmaier**, Till Kaltofen, Alexander Steger, Doris Mayr, Sven Mahner, Udo Jeschke, and Helene H. Heidegger

International Journal of Molecular Sciences, 02/2021
IF: 5,92

5-year results of a prospective multicenter trial - Advance XP for post-prostatectomy-incontinence in patients with favorable prognostic factors

Jan-Niclas Mumm, Benedikt Klehr, Severin Rodler, Alexander Kretschmer, **Theresa Vilsmaier**, Michael Chaloupka, Brigitte Ziegelmüller, Christian Gozzi, Peter Rehder, Florian May, Roland Homberg, Peter Gebhartl, Christian G. Stief, Markus Grabbert, Ricarda M. Bauer

Urologia Internationalis, 12/2020
IF: 1,69

L-Dopa-Decarboxylase (DDC) Is a Positive Prognosticator for Breast Cancer Patients and Epinephrine Regulates Breast Cancer Cell (MCF7 and T47D) Growth In Vitro According to Their Different Expression of G $_i$- Protein- Coupled Receptors

Tremmel E, Kuhn C, Kaltofen T, **Vilsmaier T**, Mayr D, Mahner S, Ditsch N, Jeschke U, Vattai A.

International Journal of Molecular Sciences, 12/2020
IF: 5,92

Development and Validation of a Novel 11-Gene Prognostic Model for Serous Ovarian Carcinomas Based on Lipid Metabolism Expression Profile

Mingjun Zheng, Heather Mullikin, Anna Hester, Bastian Czogalla, Helene Heidegger, **Theresa Vilsmaier**, Aurelia Vattai, Anca Chelariu-Raicu, Udo Jeschke, Fabian Trillsch, Sven Mahner and Till Kaltofen

International Journal of Molecular Sciences, 09/2020
IF: 5,92

The role of EP2 receptor expression in cervical intraepithelial neoplasia

Elisa Schmoeckel, Patricia Fraungruber, Christina Kuhn, Udo Jeschke, Sven Mahner, Theresa Maria Kolben, Thomas Kolben, **Theresa Vilsmaier**, Anna Hester, Helene Hildegard Heidegger,

Histochemistry and Cell Biology, 08/2020
IF: 2,62

Potential of platinum‑resensitization by Wnt signaling modulators as treatment approach for epithelial ovarian cancer

Till Kaltofen, Valentina Preinfalk, Stephanie Schwertler, Patricia Fraungruber, Helene Heidegger, **Theresa Vilsmaier**, Aurelia Vattai, Bastian Czogalla, Doris Mayr, Sven Mahner, Udo Jeschke, Fabian Trillsch

Journal of Cancer Research and Clinical Oncology, 07/2020
IF: 3,66

Frequent urination as a possibly overlooked symptom of SARS-Cov-2 positive patients -does the novel corona virus cause viral cystitis?

Jan-Niclas Mumm, Andreas Osterman, Michael Ruzicka, Clemens Stihl, **Theresa Vilsmaier**, Dieter Munker, Elham Khatamzas, Clemens Giessen-Jung, Christian Stief, Michael Staehler, Severin Rodler

Journal: European Urology, 05/2020
IF: 18,7

The prostaglandin receptor EP2 determines prognosis in EP3-negative and galectin-3-high cervical cancer cases

Dietlmeier S, Ye Y, Kuhn C, Vattai A, **Vilsmaier T**, Schröder L, Kost BP, Gallwas J, Jeschke U, Mahner S, Heidegger HH

Scientific Reports, 01/2020
IF: 4,0

Higher CCL22+ Cell Infiltration is Associated with Poor Prognosis in Cervical Cancer Patients,

Wang Q, Schmoeckel E, Kost BP, Kuhn C, Vattai A, **Vilsmaier T**, Mahner S, Mayr D, Jeschke U, Heidegger HH

Cancers 12/2019
IF: 6,16

Effects of green tea, matcha tea and their components epigallocatechin gallate and quercetin on MCF‑7 and MDA-MB-231 breast carcinoma cells

Lennard Schröder, Philip Marahrens, Julian G. Koch, Helene Heidegger, **Theresa Vilsmaier**, Thuy Phan-Brehm, Simone Hofmann, Sven Mahner, Udo Jeschke, Dagmar U. Richter

Oncology Reports, 10/2018
IF: 3,04

Anti-Müllerian hormone (AMH) levels in premenopausal breast cancer patients treated with taxane-based adjuvant chemotherapy – A translational research project of the SUCCESS A study

Trapp E, Steidl J, Rack B, Kupka MS, Andergassen U, Jückstock J, Kurt A, **Vilsmaier T**, de Gregorio A, de Gregorio N, Tzschaschel M, Lato C, Polasik A, Tesch H, Schneeweiss A, Beckmann MW, Fasching PA, Janni W, Müller V

Breast, 10/2017
IF: 3,2

Publikation zum Erwerb der eigenen Dissertation und wird für die Publikationsleistung im Habilitationsverfahren nicht gewertet

Determination of Interleuking -4, -5, -8 and -13 in Serum of Patients with Breast Cancer before Treatment and its Correlation to Circulating Tumor Cells

Alexander König, **Theresa Vilsmaier**, Brigitte Rack, Klaus Friese, Wolfgang Janni, Udo Jeschke, Ulrich Andergassen, Elisabeth Trapp, Julia Jückstock, Bernadette Jäger, Marianna Alunni-Fabbroni, Thomas Friedl, Tobias Weissenbacher, SUCCESS Study Group

Anticancer Research, 06/2016
IF: 2,06

Übersichtsartikel/Review

Gesichtslähmung nach Gemini-Geburt
J. Jückstock, **T. Vilsmaier**, J. G. Koch, T.Marx, S.Wenninger, S. Mahner, R. Kästner
Gynäkologe 07/2018

8. Acknowledgements / *Danksagung*

9. Curriculum vitae

Nicht verfügbar

10. Versicherung an Eides Statt

ERKLÄRUNG

Hiermit erkläre ich, dass die vorgelegte Habilitationsschrift selbständig ohne fremde Hilfe verfasst und die Herkunft des verwendeten oder zitierten Materials ordnungsgemäß kenntlich gemacht habe.

Des Weiteren gebe ich die Erklärung ab, dass ich bisher keine anderweitigen Habilitationen und Habilitationsversuche angestrebt habe, mir noch nie ein akademischer Grad entzogen wurde und auch kein Verfahren gegen mich anhängig ist, dass die Entziehung eines akademischen Grades zur Folge haben könnte.

München, 12.01.2022

Dr. med. Theresa Vilsmaier