

# Breast cancer and pregnancy: Challenges of chemotherapy

Miriam S. Lenhard<sup>a,\*</sup>, Ingo Bauerfeind<sup>a</sup>, Michael Untch<sup>b</sup>

<sup>a</sup> Department of Obstetrics and Gynecology, Campus Grosshadern, Ludwig-Maximilians-University of Munich, Marchioninistrasse 15, 80337 Munich, Germany

<sup>b</sup> Helios Hospital Berlin-Buch, Teaching Hospital of the Charité, Berlin, Germany

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## Abstract

**Background:** Breast cancer is the second most frequently occurring malignancy during pregnancy. As evidence-based data on diagnostics and treatment is lacking, current recommendations mostly derive from nonrandomized experiences. We reviewed the current literature with focus on chemotherapy during pregnancy and lactation.

**Results:** The diagnosis of pregnancy associated breast cancer implies the challenge to balance between a life-saving therapy for the mother's breast cancer and a potentially life-threatening therapy for the fetus. With few limitations, surgery and chemotherapy can be performed during pregnancy, preferably in the second and third trimester, whereas radiotherapy and endocrine or antibody treatment should be postponed until after delivery.

**Conclusion:** Breast cancer during pregnancy and lactation remains a therapeutic and ethical multidisciplinary challenge. Close cooperation between all disciplines is inevitable to find an optimal treatment strategy for the mother and her unborn child.

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**Keywords:** Breast cancer; Pregnancy; Chemotherapy; Systemic therapy

## 1. Epidemiology

The incidence of breast cancer at child bearing age is increasing. The so-called "pregnancy associated breast cancer" describes the diagnosis of breast cancer during pregnancy or lactation up to 1 year after delivery [1,2]. With an

\* Corresponding author. Tel.: +49 89 7095 0; fax: +49 89 7095 5844.  
E-mail address: Miriam.Lenhard@med.uni-muenchen.de  
(M.S. Lenhard).

incidence of 0.2% up to 3.8% [3,4], it represents the second most frequent malignancy associated with pregnancy. Over the last century, the age of women at primary birth has risen. In the 1970s the age of primipara in the former German Democratic Republic (GDR) was in the early twenties, while it is in the early thirties for Germany nowadays [5]. Similar data are available for Britain, whose women at first birth were 26.2 years old in 1972 and 29.1 in 2000. In combination with the fact that the breast cancer incidence increases with rising age [6], the diagnosis of pregnancy associated breast cancer will become more frequent.

## 2. Prognosis

Pregnancy associated breast cancer is mainly diagnosed at an advanced stage because its diagnosis is often delayed during pregnancy. There have been calculations showing that the risk of lymph node involvement increases by 0.028% per day based on a time of 130 days for cell doubling [7]. The delay of the diagnosis during pregnancy has been estimated at 6 months or more [8,9] according to older studies, and 1 or 2 months on the basis of newer data [10–12]. The old assumption that the prognosis of pregnancy associated breast cancer is fatal, cannot be maintained according to newer data, which have shown that there is no difference in prognosis in both collectives if tumor size, nodal status and other established prognostic markers are compared to non-pregnant women [13]. However, taking the fact into account that pregnancy associated breast cancer has mostly progressed to higher TNM-stages due to the delay of diagnosis, its general 5-year metastasis free and overall survival is worse [14].

Altogether, the weak data reflect the insufficient information which is mostly gained from retrospective studies with few patients and small control groups. In 2005, international recommendations from an expert meeting have been formulated for patients with breast cancer during pregnancy [5]. Loibl et al. compared selected studies with regard to the prognosis of patients with pregnancy-associated breast cancer and non-pregnant controls. They concluded that the worse prognosis is probably caused by the advanced stages at diagnosis or a less standardized therapy. As their data review was mostly based on case reports, case-control studies and historical cohort studies, the level of evidence is not higher than 3 with a level of evidence of 2b for chemotherapy [5].

## 3. Diagnosis

Physiological changes of the breast, especially the growing breast volume with palpable hardening, makes a palpable mass during pregnancy difficult to differentiate. A persisting mass needs to be clarified, though 80% of breast masses are benign. Among the differential diagnoses to be covered are lobular hyperplasia, fibroadenoma, cystic disease, galactocele, abscess, lipoma and hamartoma, besides very rare

disease include leukemia, lymphoma, sarcoma, neuroma and tuberculosis [8].

### 3.1. Imaging

Ideally but rarely, patients have had a previous mammography before pregnancy. In cases of unclear sonographic findings, further diagnostic imaging should be performed. Mammography, which has been analyzed best during pregnancy, is a good diagnostic tool, especially due to its ability to detect microcalcifications. Imaging detection rates range between 27% and 78% in the literature [15,16]. With new imaging equipment and techniques like digital mammography or sensitive film foilsystems and appropriate shielding, the radiation exposure for the fetus could be decreased below 0.5  $\mu$ Gy in standard bilateral mammography [17]. This dose is far below the threshold exposure of 100 mGy which is associated with a 1% risk of fetal malformations and central system problems [18]. Still, a strong indication is required for the use of X-rays in pregnant women, but with a clear indication, mammography during pregnancy can be considered safe enough.

MRI of the breast during pregnancy is still discussed controversially in the literature. A malignant hypervascularization is hard to differentiate from the physiologic hypervascularization of the breast during pregnancy and lactation, especially as there are very few studies about physiologic MR-mammography findings at this period. One advantage of this imaging modality is its avoidance of X-rays. Problematic is the use of Gadolinium in MR-imaging. It is known to cross the placenta and was associated with fetal abnormalities in animal models [19–21], and therefore pregnancy represents a clear contraindication. Without contrast media, the diagnostic value of MRI is extremely limited. During lactation, women are recommended to primarily ab lactate or stop breastfeeding for at least 24, even better 72 h after MRI to avoid Gadolinium exposure of the newborn.

Chest radiography with abdominal shielding can be judged as relatively safe during pregnancy. The expected exposure for the fetus is less than 0.01 mGy. Further staging should be carried out by abdominal ultrasound or non-contrast MRI and non-contrast thoracic-lumbar MRI [22]. According to present recommendations, MRI can be performed safely during pregnancy [20,23–25]. A routine bone scintigraphy or CT-imaging should not be used in pregnancy, especially not in early gestational week, due to high irradiation doses to the fetus [5,18].

### 3.2. Pathology

Persistent or suspicious lesions in imaging should be further evaluated: solid findings should be biopsied, cystic or liquid findings should be analyzed by cytology [26]. The definite diagnosis of breast cancer has to be made by core needle biopsy [27]. The risk of misdiagnosis due to the hyperproliferative changes of pregnancy in the breast tissue can be reduced

if the pathologist is told about the patient's pregnancy. Moreover, the histologic result highly depends on the pathologist's experience with pregnancy-associated breast cancer [27,28]. Therefore, a second opinion slide review by another experienced pathologist can be recommended.

There are hardly any complications from the biopsy procedure during pregnancy or lactation [29], although the risk of bleeding is increased due to hypervascularization of the tissue, and the risk of infection is also slightly higher. Sometimes ablactating is recommended in these cases [30].

## 4. Treatment

### 4.1. Local therapy

Surgery in pregnant women can be performed nearly equally as in non-pregnant patients. The first trimester is critical in terms of a higher rate of spontaneous abortions, especially the first 12 weeks. Depending on the gestational age, monitoring of the fetus should be conducted. So far, there is a higher rate of mastectomy among patients with breast cancer during pregnancy. This fact can be explained for different reasons: due to the larger tumor size in general, breast-conserving therapy is only in limited cases possible. Moreover, there has been the discussion in the past that mastectomy will minimize the likelihood that adjuvant radiation is necessary [31]. However, according to the current recommendations for adjuvant therapy, radiotherapy is indicated for patients with tumors larger than 3 cm, T3/T4 TNM-stage, pectoralis fascia infiltration, margins off less than 5 mm in sano, multicentric tumors, lymph node infiltration or if there is lymph- or hemangiosis carcinomatosa. The current guideline of the German Consensus-Conference proposes additionally a radiotherapy if tumors consist of large in situ-components, G3 differentiation, hormone receptor negativity, multifocality, diffuse microcalcification or age under 35 years. Regarding breast conserving therapy and mastectomy, no difference has been found for disease free and overall survival by a study by Kuerer et al. [32].

Axillary lymph node dissection is indicated like in non-pregnant patients with breast cancer. Due to the reduction of morbidity, there is a generally rising interest in sentinel node biopsy. Besides a higher prevalence of contraindications in this patient due to a higher rate of too large (>2 cm) tumors, multicentricity or palpable lymph nodes, there are other contraindications for pregnant women. The use of radioactive substances is critical in pregnancy in general, though the dose of 12 MBq of <sup>99m</sup>Tc-HAS should be a low assumed risk for fetal irradiation, which was analyzed by Gentilini et al. [33].

Alternatively, blue-staining alone can be used, but a high expertise with the sentinel method by the operating physician is required to apply this method alone sufficiently. If sentinel-node biopsy is performed properly, there seems to be little risk for the fetus in terms of prenatal death, malformation or mental impairment [33]. Until more data is available, sen-

tinell node biopsy should not be used as standard in pregnant women [34].

Even with mastectomy, there very often is an indication for radiotherapy after breast surgery in patients with pregnancy associated breast cancer. The fetal sensitivity to radiation depends on the dose and time of exposure. The most sensible period is the time of organogenesis, especially the first 50 days after conception, where malformations can occur at doses higher than a threshold of 100–200 mGy [35]. Malformations become more unlikely after the 8th gestational week, the time in pregnancy when the fetus is becoming susceptible for neurological defects [36]. A decrease of the fetal IQ has been observed at doses higher than a threshold at 0.1–0.2 Gy during the 8–25 weeks. A risk of mental retardation has to be assumed if the exposure of the unborn child rises to 1 Gy [18,37]. Also, observations from diagnostic X-ray imaging during pregnancy have shown an increased risk of cancer during childhood from fetal doses in the order of 10 mGy and a coefficient of about 6% per gray [38].

There are case reports of women who received radiotherapy of the breast and proper shielding during pregnancy, which did not entail any malformations for the fetus [37]. Nonetheless it is still recommended to postpone radiotherapy until after delivery, especially as there is data showing that the delay of radiotherapy by up to 3 months is of no prognostic disadvantage for patients with breast cancer [39,40].

### 4.2. Systemic therapy

Many women with pregnancy-associated breast cancer present at an advanced stage of disease and therefore have to be treated with adjuvant or neoadjuvant chemotherapy. In pregnancy, most chemotherapeutic agents are classified into the Category D [41–43,44]. The correct dosing of chemotherapy in pregnant women is complicated by the fact that plasma volume, hepatorenal function or albumin concentration change during pregnancy. Most recommendations for chemotherapy dosing solely take body weight into account. Interestingly, studies have shown no BMI related disadvantage for the receipt of appropriate primary breast cancer therapy [45].

Major complications have been described with an incidence around 3% after exposure to cytotoxic drugs in utero, which is only slightly elevated compared to the average risk of 2–3% in the general population [46]. The teratogenic risk highly depends on the time of application and chemotherapeutic agent. Complications often seen after chemotherapy in utero comprise intrauterine growth restriction, preterm delivery, low birth weight or transient leucopenia. Chemotherapy during the first trimester, when organogenesis takes place, can be associated with spontaneous abortion or increased risk for severe fetal malformation. Fetal malformations occur with an incidence of 14–19%, depending on the chemotherapeutic agents, when administered in the first trimester, while the frequency drops to 1.3% thereafter [47]. A French national survey reported two women who were treated with

chemotherapy in the first trimester, and both patients had an abortion [48]. Therefore, chemotherapy should be avoided in the first trimester.

Because of the high teratogenicity at this time of pregnancy, the question of abortion was raised and further discussed in terms of an adequate, prompt therapy for the mother [47,49]. There are studies that show no difference in the prognosis of the mother if an abortion has taken place [1,50,51].

In the second and third trimester, the use of chemotherapy does not seem to increase the risk of fetal malformations. The choice of chemotherapeutic medication remains difficult regarding the scarcity of information on the children's long-term outcome, leaving the treating physician in the ethical conflict to take care of an adequate cancer therapy but to protect the unborn from a potentially harmful treatment [52]. In an 18-year experience gained at five London teaching hospitals, none of the 27 children whose mothers were treated for breast cancer in utero at second or third trimester showed congenital malformations [44]. Chemotherapy-regimes were CMF (cyclophosphamide, methotrexate, fluorouracil)-based in 12 cases and antracycline-based in the others. In this series, one spontaneous abortion occurred in a patient treated with CMF-chemotherapy in her first trimester of pregnancy [44]. The largest cohort describing 84 children whose mothers were treated with combined chemotherapy for hematological malignancies during pregnancy showed a normal physical, neurological and physiological development at a median follow-up of 18.7 years. Moreover, no childhood cancer was reported in the first or second-generation children [53].

A study from the MD Anderson Cancer center reports 57 women with pregnancy associated breast cancer who were treated with FAC (fluorouracil, doxorubicin, cyclophosphamide) chemotherapy in an adjuvant or neoadjuvant setting [41]. Median follow-up was 38.5 months. Children exposed to chemotherapy in utero showed no significant short-term complications when exposed in the second or third trimester. There were no cases of still-births, miscarriages or perinatal deaths that could be related to therapy. Three children were born before the 34th week, with one infant delivered at less than 29 gestational weeks due to maternal preeclampsia. One child was born with Down's syndrome. Neonatal complications included difficulties in breathing with 10% requiring mechanical ventilation. There was one documented case of hemorrhage 2 days after delivery, going along with thrombocytopenia and neutropenia at that time. Altogether, the birth weight was less than 2500 g in six newborns. Long-term results have still to be awaited to analyze effects on fertility or cardiac function. A survey of 18 school-age children showed a normal development in 16 cases, with two children needing special support [41].

The use of methotrexate during pregnancy is contraindicated, as it is described to induce severe malformations known as the "aminopterin syndrome" [47,54]. This syndrome is associated with prenatal-onset growth deficiency, severe lack of ossification of the calvarium, prominent eyes secondary to

hypoplastic supraorbital ridges, small, low-set ears, micrognathia, and limb abnormalities [55]. Moreover, it can induce abortions and is used in the treatment of hydatid mole, chorion carcinoma or trophoblastic persistence [26,54].

Antracyclines are judged to be relatively safe, but they pass the placenta and also contaminate the breast milk [56,57]. Moreover, there are still concerns of antracycline-associated fetal cardiotoxicity. Exposure with idarubicin or epirubicin in utero has been suspected to entail neonatal cardiac effects and even deaths in utero [48,56,58]. Idarubicin favors placental transfer due to its lipophilic character. In pregnancy, idarubicin should not be administered, as there have been four cases of fetal or neonatal deaths out of 17 treated cases and further two descriptions of transient cardiomyopathy, after administration of epirubicin and idarubicin. On this basis, epirubicin and idarubicin should not be administered during pregnancy [43].

Regarding the cardiotoxic risk there is one study in which echocardiograms were performed every second week in pregnant women undergoing a chemotherapy with doxorubicin and cyclophosphamide. The fetus was monitored beginning at the 24th gestational week and data were compared to untreated healthy mothers at 20th to 40th week of pregnancy. Neither short-term results for systolic function nor 2-year follow up for myocardial damage showed a significant difference between both study groups [59].

The role of taxanes in chemotherapy is still unclear. The data for taxanes is mainly based on case reports (Table 1) and are therefore not meaningful to support its safety, especially not in combination with antracycline-based chemotherapy regimens [60–64]. There is data postulating paclitaxel and vincalkaloids to be safe after the first trimester, as these tubulin-binding agents can be bound by the high placental expression of drug-extruding transporters like P-glycoprotein (PgP) or BCRP-1 [65]. Fetal drug exposure increases dramatically by absence or pharmacological blocking of placental PgP [66].

In the French national survey, there were 18 patients who received a variety of chemotherapy regimens, including four patients treated with vinorelbine [48]. No fetal malformation occurred in this patient group whose fetus were exposed during the second and third trimester [48].

There is no sufficient information about the use of trastuzumab during pregnancy. In the literature there are few cases of in utero exposure. One case report [67] described a reversible oligohydramnios, another two an anhydramnios [68,69] No relevant direct fetal toxicity has been described by [70], who noticed a reversible maternal heart failure under trastuzumab treatment during pregnancy. Still, all running studies recommend stringent contraception under trastuzumab treatment and advise not to get pregnant within 3 months after therapy.

There are hardly any reports of antibody treatment other than trastuzumab during pregnancy. One case of approximately 11 weeks of lapatinib exposure during the first and second trimester has been reported. The patient got pregnant

Table 1  
Taxane treatment for breast cancer during pregnancy adapted from Mir et al. [64]

Reference	Treatment regimen	Initiation of treatment	Abnormalities during pregnancy	Neonatal status	Infants development
<b>Docetaxel</b>					
De Santis et al.	V 25 mg/m <sup>2</sup> followed by D 100 mg/m <sup>2</sup> (three cycles)	NR	NR	Apgar 8, 9	Healthy at 20 m
Gainford et al.	D 35 mg/m <sup>2</sup> weekly (5 weeks)	32	NR	Healthy	Healthy at 15 m
Potluri et al.	AC followed by D 75 mg/m <sup>2</sup> q 15 days (four cycles)	26	Hydrocephalia (with AC)	Hydrocephalia	Healthy at 28 m
Potluri et al.	Doxorubicine 60 mg/m <sup>2</sup> and D 75 mg/m <sup>2</sup> (six cycles)	14	NR	Healthy	Healthy at 9 m
Nieto et al.	FAC followed by D 100 mg/m <sup>2</sup> (four cycles)	25	Hand-foot syndrome	Healthy	NR
Sekar et al.	D 190 mg and Trastuzumab (three cycles)	23	Anhydramnios at 30 weeks, fetal growth restriction (5th percentile)	Apgar 7, 9	NR
<b>Paclitaxel</b>					
Bader et al.	Trastuzumab and P 175 mg/m <sup>2</sup> (two cycles)	25	Anhydramnios	Bacteremia, NRD	Healthy at 3 m
Gadduci et al.	Epirubicin 120 mg/m <sup>2</sup> (four cycles) followed by P 175 mg/m <sup>2</sup> (three cycles)	25	NR	Normal CBC	Healthy at 36 m
Gonzals-Angulo et al.	Weekly P 80 mg/m <sup>2</sup> (12 weeks)	21	NR	Apgar 9, 9	Healthy at 12 m
Lycette et al.	AC (two cycles) followed by P 175 mg/m <sup>2</sup> and GCSF (four cycles)	30	Transitory contractions after 2nd cycle	Twins: Apgar 7, 8 and 8, 9	Healthy at 16 m

(AC, adriamycin/cyclophosphamide; D, docetaxel; FAC, 5-fluorouracil/adriamycin/cyclophosphamide; P, paclitaxel; V, vinorelbine; GCSF, granulocyte-colony stimulating factor; CBC, complete blood count; NRD, neonatal respiratory distress; NR, not reported; m, months).

while she was treated on a phase I clinical trial for lapatinib. In this case no complications in utero were reported and a healthy baby was born [71].

Only little is known about the use of an anti-hormonal therapy during pregnancy. There are few reported cases of tamoxifen exposure in utero [67]. No fetal toxicity was observed in patients with metastatic breast cancer, but there has been the association of ambiguous genitalia and Goldenhar's syndrome when applied during pregnancy [72–77]. In female mice, tamoxifen has been shown to cause neonatal defects in the genital tract [78]. Altogether, tamoxifen is not recommended during pregnancy, but anti-hormonal therapy is indicated after delivery and completion of chemotherapy.

The palliative situation of pregnancy associated breast cancer is very difficult. As the breast cancer cannot be treated curatively, the side effects of therapy for the fetus should be held as low as possible. Chemotherapy may be inevitable if, e.g. visceral metastases occur. In this situation, a mono-therapy should be preferred, with a priority of antracyclines.

## 5. Supportive care

Steroids, 5HT3-serotonin antagonists or granulocyte colony-stimulating factors (G-CSF) are often part of supportive treatment of antracyclin-based chemotherapy. Ozer et al. [79] have shown G-CSF to be safe during pregnancy, if used according to standard recommendations for growth factor support. The 5HT3-serotonin antagonist ondansetron has been tested in animal models at dosages much higher than in humans. At these concentrations there were no developmental toxicities described. Tincello et al. analyzed the use of ondansetron in pregnant women and rated it as safe in the first trimester [80]. Exposure of corticosteroid in the first trimester has been recognized to cause a statistically significant higher number of cleft palate and should therefore not be used at this time of pregnancy (LOE 3b) [5]. As most women with pregnancy-associated breast cancer are treated with chemotherapy at later stage of pregnancy, the second or third trimester, ondansetron and corticosteroids seem to be applicable without relevant risk of fetal malformation.

## 6. Multidisciplinary management

Therapeutic strategies for breast cancer during pregnancy or the lactation period require a medical environment including gynecologists, oncologists, radiologists, surgeons, pediatricians and pathologist who develop individualized treatment regimes.

Genetic breast cancer occurs at a younger age compared to sporadic breast cancer, and therefore women with pregnancy associated breast cancer are more likely to have an inherited form of cancer. Therefore, women should be given the option of genetic counseling and testing for BRCA-1 and -2. There

is data showing that there is a higher prevalence of BRCA-1 mutation compared to BRCA-2 mutations [81].

The diagnosis of breast cancer is an emotionally exhausting situation, not only for the patient but the whole social surrounding, especially close family and friends. Psychological counseling should be available when patients are confronted with the stressful new situation especially if patients find themselves in a conflict between own treatment and protection of their unborn child.

## 7. Monitoring of the pregnancy

Prenatal care in women diagnosed with breast cancer during pregnancy should be performed just like in other pregnant women. To correctly estimate the fetus' risk caused by the mother's cancer treatment, it is essential to clearly define the gestational age and status of the fetus before the beginning of therapy. Nonetheless, it is recommended to supervise women undergoing chemotherapy during pregnancy closely to intervene early if the fetus is at risk in utero. The time of delivery should be balanced according to the need of breast cancer treatment and the maturation of the fetus. The mode of delivery should be discussed according to available medical infrastructure, the patient's previous obstetric history and own preferences. Vaginal birth holds a lower risk of maternal morbidity compared to cesarean section [82] and might be preferable if further chemotherapy is planned, because it comprises a lower risk of therapy delay.

Even though there is so far no case of metastases of breast cancer to the fetus, there have been reports of placental metastases [83–85]. The placenta should therefore be analyzed histopathologically after delivery [86,87].

Preservation of fertility is an important issue for women diagnosed with pregnancy-associated breast cancer. As these women are still at child bearing age, the question of further pregnancies has to be addressed before starting a chemotherapy, which can cause amenorrhea in a high percentage. Depending on the chemotherapy regimen, there are different rates of amenorrhea described [75]. There is data of women under 40 years of age showing that 18–61% of cyclophosphamide-based treated women suffer from amenorrhea; after anthracycline-based regimens it is described to be 30–60% [75].

In terms of fertility, there is only insufficient experience after the use of taxanes, especially as it is often used sequentially or consecutively to either cyclophosphamide- or anthracycline-based treatment. Even though it seems preferable for the women's further family planning to stay fertile, there is data showing a positive correlation of amenorrhea and disease-free and overall survival [75].

Prospective randomized studies for the treatment of pregnant women with breast cancer are not expected for the near future due to the rarity and specialty of this disease. Altogether, a pregnancy after cancer treatment is always to be

supported if the mother feels mentally and physically strong enough to carry out a pregnancy.

## Conflict of interest statement

There exist no financial or personal relationships with other people or organisations that could inappropriately influence this work. There are no employment, consultancies, stock ownership, honoraria, paid expert testimony, patent applications/registrations, grants or other funding influencing this work. Neither of the authors holds a conflict of interest.

## Reviewers

PierFranco Conte, MD, Director, Dept. of Oncology and Hematology, University Hospital, Modena, Via Del Pozzo, 71 IT-Modena, Italy.

Gunter Von Minckwitz, MD, PhD, Zentrum der Frauenheilkunde und Geburtshilfe, J.W. Goethe Universität, Theodor-Stern-Kai 7, D-60590 Frankfurt, Germany.

Pierre-Alain Brioschi, MD, Responsible of Gynecology and Senology, Clinique de Genolier, 1, route du Muids, CH-1272 Genolier, Switzerland.

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## Biography

*Dr. Lenhard* studied medicine at Wuerzburg University, Zuerich University and Harvard Medical School. She graduated in 2003 and received the medical doctor summa cum laude in 2005, winning the prize of the medical faculty of the University of Wuerzburg. She also graduated in medical economics in 2003. Since 2003, Dr. Lenhard is a gynaecologist at Grosshadern Hospital of the Ludwig Maximilians University of Munich. Her main areas of interest and research are gynecological oncology with a focus on ovarian cancer and breast cancer.