Breast Cancer (Mammary Carcinoma) — Causes, Classification and Symptoms

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Breast cancer (mastocarcinoma) is the most common form of cancer among women. Consequently, it will be encountered by doctors as part of their work in hospitals and medical practice. This disease exhibits a heterogeneous pattern including different histological subtypes, which may differ considerably in their degree of malignity and, consequently, in their clinical symptoms and therapy. The following article helps you to understand the clinical picture of mastocarcinoma, identify its symptoms and to classify its histology correctly.

Definition of Breast Carcinoma

The breast cancer, also known as mastocarcinoma, is a malignant tumor of the breast (mammary gland).

The point of origin of breast cancer may either be the mammary gland’s ducts or the lobules. Correspondingly, the two common breast cancer types, ductal carcinoma and the lobular carcinoma, are differentiated.
The breast cancer is the most common form of cancer among women, accounting for 29% of all malignant diseases among women in the United States. The yearly incidence adds up to 110 cases per 100,000 women.

More than 90% of diagnoses occur in women over 40 years of age, while the median age at the time of diagnosis of breast cancer is 61 years.

**Note:** One out of 8 to 10 women gets breast cancer during her lifetime! The chances of becoming diseased with breast cancer increase with age, but young women also can be affected. It usually affects women between the ages of 60 – 80 years.

**Note:** In the western hemisphere, the most common cause of death among women in their 35th – 55th year of life is the breast cancer!

However, not only women get breast cancer: 1% of breast cancers affect men.
Etiology of Breast Cancer

Causes of the breast cancer

The exact etiology of breast cancer is unknown, but it is assumed to be a multifactorial event. The majority of breast cancers forms spontaneously (= sporadically, about 95%), whereas only a minor fraction is of hereditary origin, in terms of familial genetic modifications (about 5%).

Risk factors for the breast cancer

There are multiple risk factors, which may promote the formation of breast cancer.

*The most important population-related risk factor for the formation of breast cancer is advanced age.*

With advanced age, the risk of contracting breast cancer increases. The other common risk factors include hormonal influences (endogenous or exogenous), positive family history (genetic predisposition), obesity, nulligravida, early menarche, late menopause, diet and lifestyle. The following table gives you an overview:

<table>
<thead>
<tr>
<th>Risk factors</th>
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<tbody>
<tr>
<td><strong>Diet/lifestyle</strong></td>
<td>Large amounts of meat and fat, overweight/obesity (especially after menopause), high intake of alcohol and cigarettes</td>
</tr>
<tr>
<td><strong>Family history</strong></td>
<td>Breast cancer in first or second-degree relatives (mother, grandmother, sister), Ashkenazi Jewish descent.</td>
</tr>
<tr>
<td><strong>Hormonal influences</strong></td>
<td>Long hormone exposure: early menarche and late menopause; higher age at first delivery (&gt; 30 years of age), nulliparity, hormone replacement therapy after menopause (&gt; 5 years), oral contraceptives (disputable)</td>
</tr>
<tr>
<td><strong>Others</strong></td>
<td>Breast cancer on contralateral side, ionizing radiation, benign findings in a biopsy, mastopathy, hyperprolactinemia</td>
</tr>
</tbody>
</table>

In the majority of hereditary breast cancers, a mutation on one of the following two tumor suppressor genes can be found. These genes are the “BReast-CAncer 1 and 2” BRCA-1 (on chromosome 17q) and BRCA-2 (on chromosome 13q).
Note: Women with BRCA-1 or BRCA-2-gene mutations have a higher risk (80 – 90%) of breast cancer. These women also have increased risk for ovarian cancer.

Classification of Breast Carcinoma

WHO-classification

The World Health Organization (WHO) classifies breast cancer into ductal and lobular carcinomas histopathologically on the basis of their origin. This classification covers invasive breast cancers as well as precursor lesions, lesions of low malignant potential, and benign lesions.

Note: The 80% of breast cancers are ductal carcinomas, while around 20% are lobular carcinomas. The following is an over-simplified overview of the WHO-classification:

| Invasive breast carcinomas | • Invasive carcinoma of no special type (NST)  
|                           |   • Invasive lobular carcinoma  
|                           |   • Tubular carcinoma  
|                           |   • Cribriform carcinoma  
|                           |   • Mucinous carcinoma  
|                           |   • Carcinoma with medullary features  
|                           |   • Carcinoma with signet ring differentiation  
| Epithelial-myoepithelial tumors | • Pleomorphic adenoma  
|                              | • Adenomyoepithelioma  
| Precursor lesions            | • Ductal carcinoma in situ  
|                              |   • Lobular neoplasia  
|                              |   • Lobular carcinoma in situ  
|                              |   • Atypical lobular hyperplasia  
| Papillary lesions            | • Intraductal papilloma  
|                              | • Intraductal papillary carcinoma  
|                              | • Encapsulated papillary carcinoma  
|                              | • Solid papillary carcinoma  
| Benign epithelial proliferations | • Sclerosing adenosis  
|                                 | • Apocrine adenosis  
|                                 | • Microglandular adenosis  
|                                 | • Radial scar / complex sclerosing lesion  
|                                 | • Adenomas  
| Fibroepithelial tumors        | • Fibroadenoma  
|                                 | • Phyllodes tumor  
|                                 | • Hamartoma  
| Tumors of the nipple          | • Nipple adenoma  
|                                 | • Syringomatous adenoma  
|                                 | • Paget disease of the nipple |
TNM-classification of the breast cancers

The **TNM-classification** is an important instrument to classify malignant tumors with regard to their spreading, affection of **regional lymph nodes** and the presence or absence of **distant metastases**. Using this classification, the prognosis and the treatment strategy is determined.

The following table depicts the TNM-classification of the mastocarcinoma using the classification of the UICC (Reference: Diagnostic Breast Center Munich).

<table>
<thead>
<tr>
<th>Primary tumor (T)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor ≤ 20 mm in greatest dimension</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor &gt; 20 mm but ≤ 50 mm in greatest dimension</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor &gt; 50 mm in greatest dimension</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor of any size with direct extension to the chest wall and/or to the skin (ulceration or skin nodules)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Regional lymph nodes (N)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
<td>Regional lymph nodes cannot be assessed (eg, previously removed)</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Metastasis to movable ipsilateral level I, II axillary lymph node(s)</td>
</tr>
<tr>
<td>N2</td>
<td>Metastases in ipsilateral level I, II axillary lymph nodes that are clinically fixed or matted or In clinically detected ipsilateral internal mammary nodes in the absence of clinically evident axillary lymph node metastasis</td>
</tr>
<tr>
<td>N3</td>
<td>Metastases in ipsilateral infraclavicular (level III axillary) lymph node(s), with or without level I, II axillary node involvement, or In clinically detected ipsilateral internal mammary lymph node(s) and in the presence of clinically evident level I, II axillary lymph node metastasis.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Distant metastasis (M)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>No clinical or radiographic evidence of distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Distant detectable metastases as determined by classic clinical and radiographic means and/or histologically proven &gt; 0.2 mm</td>
</tr>
</tbody>
</table>

Pathology and Pathophysiology of Breast Cancer

Histological examination of breast cancer
As already mentioned, the breast cancer is classified in ductal or lobular and invasive or non-invasive (in-situ) types. The ductal carcinoma in-situ (DCIS) and the lobular carcinoma in-situ (LCIS) remain locally and do not break through the basal membrane, whereas invasive carcinomas infiltrate the surrounding tissues. After a period of latency, the in-situ-carcinomas may develop into an invasive carcinoma. The most frequent one is the adenocarcinoma.

The DCIS originates from the ducts of the mammary gland and may be differentiated differently: solid (most frequently), comedo-type, cribriform or papillary. The various subtypes are different in their progression, prognosis and therapy.

In the case of the DCIS central necrosis may develop into calcium-precipitation ("micro-calcification"), which can be critical for diagnostics. The period of latency of the invasive ductal carcinoma is about 10 years.
The **LCIS** originates from monomorphic cell proliferation with small tumor cells in the **lobules** of the mammary gland. The acini extend to a bulb-shaped form. The **period of latency** before transformation into an invasive lobular carcinoma is, being up to 25 years, longer than the period of latency of the DCIS, for which reason the LCIS is also named a **pre-cancer**. Often it is **multi-centric**.

### Clinical Symptoms of Breast Cancer

#### Localization and metastasis of the breast cancer

The breast cancer is most frequently located (55%) in the **upper outer quadrant** of the breast due to increased breast density, whereas it is located **retro-areolar** in 15%, in the **upper inner** in 15% and in the **lower outer quadrant** in 10% of the cases. The **lower inner quadrant** is affected very rarely, amounting to only 5%.

A carcinoma is said to be **multifocal** if multiple foci in the same quadrant are present. If it is **multi-centric**, different quadrants of the breasts are affected. Furthermore, in 5 – 10% of cases, the **contralateral** breast is also affected by the tumor.

Breast cancers can **metastasize** at an early stage through lymphogenous and/or hematogenous routes:
Lymphogenous metastasis is into the regional lymph nodes of the axilla, while the hematogenous spread is into the skeleton (most common), lung, liver or brain. Also, metastasis into the ovaries is possible.

Affected axillary lymph nodes are used as an indicator of a hematogenous metastasis. During further procedures, examinations that verify metastases in organs should follow. For this, a chest X-ray, ultrasonic examination of the liver and bone scintigraphy is used.

Symptoms of the breast cancer

The breast cancer is often asymptomatic in early stages. A dense palpable lump in the breast, which is detected by the patient herself in the majority of cases, is the leading symptom of the breast cancer. Further symptoms are the following:
- Changes in size, shape, and symmetry of the breast
- Eczema of the nipple (always needs clarification!)
- Skin changes in color or texture
- Dimpled skin (plateau phenomenon)
- Orange-peel-skin (peau d’orange)
- Retraction of the nipple
- Bloody nipple secretion
- Swollen axillary lymph nodes
- Localized chest pain (rarely)

**Note:** A palpable node always needs to be tested.

**Special Types of Breast Cancer**

The special types of the breast cancer, **inflammatory breast cancer** and the **Paget’s disease** of the nipple, are outlined briefly in the following section.

**Inflammatory breast cancer**

The inflammatory breast cancer is rare and aggressive type of breast cancer that is characterized by **erythema** and **pitting** of the skin, **orange-peel-skin**, and **breast swelling**.
(a) inflammatory breast cancer (IBC) case (b) IBC; erythema, edema and peau d’orange of the right breast, no tumor mass, duration of signs is 1 month; (c) IBC; erythema, edem, peau d’orange of the left breast, duration of signs is 12 months. (d) IBC; erythema, edema, peau d’orange of the right breast, duration of signs 72 months.” von openi. License: [CC BY 2.5]

It is accountable for 1 – 4% of all breast cancers. It is often hard to diagnose due to lack of a defined palpable tumor. Mammography and sonography often do not deliver distinct results.

Therapy includes neoadjuvant chemotherapy or radiation to be followed by surgery (modified radical mastectomy). Having a 5-year-survival-rate of only 5%, the prognosis of the inflammatory mastocarcinoma is poor.

Paget’s disease of the nipple

The Paget’s carcinoma grows intraepidermal ductal and appears in an eczematously changed nipple and/or areola. It may be accompanied a DCIS or an invasive ductal carcinoma.

Since mammography is usually without pathological findings, exfoliative cytology is a proper way to detect the typical Paget-cells (large cells, bright cytoplasm, and large round/oval nucleus). MRI-scans can be equally sensible.

For therapy, the modified radical mastectomy and, in individual cases, a breast-preserving therapy (BPT) comes into consideration, in which the therapy plan depends on
the present type of carcinoma.

![Image: "High magnification micrograph of extramammary Paget's disease, abbreviated EMPD" by Nephron. License: (CC BY-SA 3.0)](image)

**Note:** With an eczematous nipple, Paget's disease should always be ruled out!
The further diagnostic and therapeutic steps can be found in the next article: The mastocarcinoma II – diagnosis, therapy and prognosis.

**Review Questions**

The correct answers can be found below the list of references.

**Which of the named transformations is least typical of the typical clinical picture of breast cancer?**

A. Bloody fluid leaking out the nipple
B. Swollen axillary lymph nodes
C. Multiple lumps inside the breast
D. Peau d’orange
E. Eczematous transformation of the nipple

**Which is the correct statement?**

A. Most frequently, breast cancer is located in the lower outer quadrant.
B. Men cannot get breast cancer.
C. Every 8th to 10th woman gets breast cancer during the course of her life.
D. The patient's age plays a minor role in the formation of breast cancer.
E. Breast cancer metastasizes late.

**A 52-year old patient presents with a redness and swelling of her left breast. According to the patient, this has developed slowly. During the examination, you notice hyperthermia of her left breast in comparison to her right one. Which diagnosis is the most likely?**

A. Paget's disease of the nipple
B. Nonpuerperal mastitis
C. Comedo-like DCIS
D. Inflammatory breast cancer
E. Multifocal breast cancer
References


**Correct answers:** 1C, 2C, 3D

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