Breast Cancer: Diagnostic Imaging and Therapeutic Guidance

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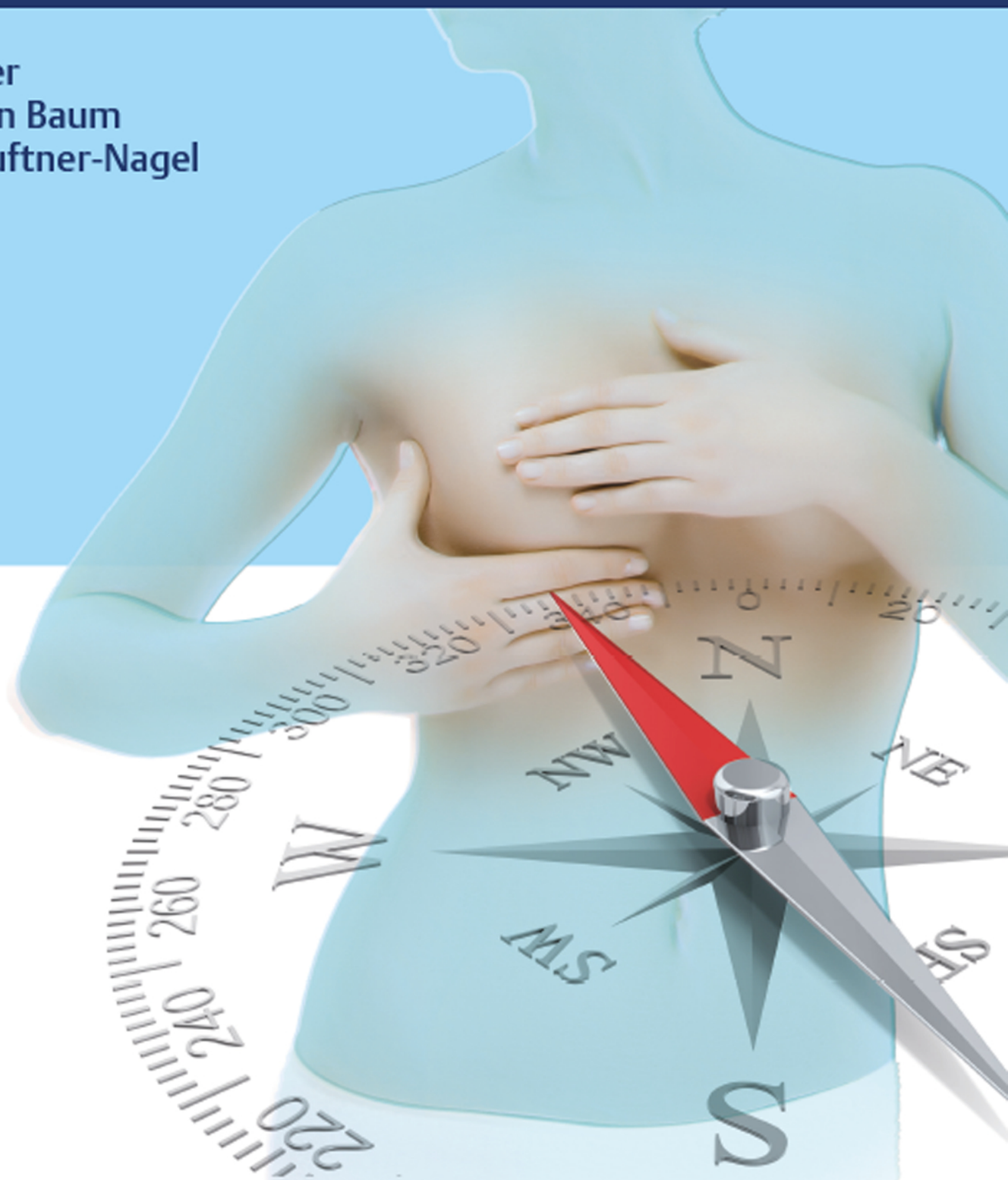

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Preface

Carcinoma in the female breast is a frequent finding in routine patient care, as it is the most common form of cancer in women. Breast cancer is a complex illness. Physicians of various specialties (e.g., radiology, gynecology, surgery, oncology) are involved with its many different aspects and our knowledge of the disease is presently growing at an incredible rate.

Advances made in recent years in the diagnosis and therapy of breast cancer pertain in large part to the study of etiological factors that increase the likelihood of developing the disease. Most of what we know about inherited breast cancer risk, for example, is based on research done in the past 10 to 15 years. There is no end in sight to the knowledge that can be gained concerning the genetic predisposition to diseases. Revolutionary progress has also been made recently in the field of diagnostic imaging. Digital mammography and modified mammographic techniques, improvements and innovations in ultrasound diagnostics, and, in particular, developments in breast MRI enabling the acquisition of high-resolution images have broadened the spectrum of available imaging procedures and dramatically improved the accuracy of breast cancer diagnosis. In addition to individualized and risk-adapted early diagnosis concepts, nationwide, population-based early diagnosis programs have been introduced. Moreover, there are now image-guided techniques available for all imaging modalities that enable the performance of reliable, low-risk, outpatient biopsies. This has sharply reduced the rate of unnecessary operations undertaken for diagnostic excision. In the field of surgery, too, there have been numerous changes and improvements. One of the greatest new advances in recent years has been the introduction of the sentinel lymph node biopsy technique, which spares many patients the burden of an unnecessary extensive lymphadenectomy, with its potential for complications. In addition, an increased range of breast-conserving operations and improved plastic-reconstructive surgical techniques are available to today's patients.

As might be expected, the approaches used in adjuvant medication and radiation therapy for treatment of breast cancer have changed and developed as well. The continual integration of new research and study results effects a constant modification and optimization of the relevant treatment concepts. Consequently, it becomes more difficult all the time for practitioners who are not directly involved in the diagnostics or treatment of breast diseases to keep up with the latest information on the topic of breast cancer.

Our aim in publishing this book is to create a reference work for physicians who are not directly involved with breast health, as well as for interested specialists and students. It gives a comprehensive overview of the most important aspects of breast cancer diagnosis and therapy, so that any unfamiliar aspects or terms can be looked up easily and understood rapidly. The emphasis here is on a succinct presentation of the facts, guidelines, and recommendations as we know them today.

Because guidelines and recommendations vary between different countries and continents, the authors have agreed in this book to present European—i.e., German—recommendations as appropriate. In general, we have deliberately chosen not to provide lengthy explications of background information.

In preparing the chapters on diagnostics and therapy of breast cancer, we were particularly pleased to have the privilege of working with Professor Clemens F. Hess, radiotherapist and radiation oncologist; Professor Guenther Emons and his leading senior physician, Dr. Martin Hellriegel, gynecologist and gynecological oncologist; Dr. K. P. Hermann, physicist specializing in mammography; and all of the participating staff at the Women's Health Care Center in Göttingen, to create what is in essence a "Göttingen Breast Book." This is significant because Göttingen's own university medical center has for decades now made the diagnosis and treatment of breast cancer a high priority in both research and patient care.

Our particular thanks also go out to the "external" colleagues who worked with professionalism and passionate commitment to help make this book a success. First of all there is Dr. Heike Lorch, who, together with Ms. Jutta Rueschof and Ms. Anke Kuechemann, did such excellent work in preparing the chapter on counseling techniques and psychosocial guidance for women with breast cancer. Their wealth of experience and empathy shine through unmistakably. Furthermore, we extend our heartfelt thanks to Professor Thorsten Kuehn, who unfortunately no longer works in the vicinity of Göttingen. His extensive experience and pragmatic approach to breast surgery have given this book—like our previous book on breast intervention—a special additional value. We also wish to thank Professor Josef Rueschof most heartily for bringing structure and a clear overview, in his inimitable style, to the histopathological intricacies and details of breast pathology. His manner of combining text and images makes it possible for the reader to quickly grasp the morphological aspects of breast disease. In conclusion, a word to our own department: We have thoroughly enjoyed writing another book with you, Susi (a.k.a. Dr. Luftner-Nagel); discussing, critiquing, and modifying the contents, and ultimately agreeing on the final version. Thank you so much.

We hope our readers enjoy this "breast book," and wish them every success in the rapid clarification of questions on the topic of the breast.

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Abbreviations

ABVS	automated breast volume scanner
ACR	American College of Radiology
ADH	atypical ductal hyperplasia
AFIP	Armed Forces Institute of Pathology
AGD	average glandular dose
AGO	Arbeitsgemeinschaft für gynäkologische Onkologie (Working Group for Gynecological Oncology)
ALD	axillary lymph node dissection
AJCC	American Joint Committee on Cancer
ALH	atypical lobular hyperplasia
ARNO 95	Arimidex-Nolvadex 95
ATAC study	Anastrozole, Tamoxifen Alone or in Combination
BCT	breast-conserving therapy, breast-conserving surgery
BIG	Breast International Group
BI-RADS	breast imaging reporting and data system
BRCA genes	breast cancer genes
BSA	body surface area
BW	body weight
BZG	Diagnostisches Brustzentrum Göttingen (Women's Health Care Center Göttingen)
CAD	computer-aided diagnostic system; computer-assisted detection; computer-aided diagnostics
CCC	comprehensive cancer center
CCD detector	charge-coupled device detector
CC projection	craniocaudal projection
CD	cluster of differentiation
CDMAM phantom	contrast detail mammography phantom
CK	cytokeratin
CLIS	carcinoma lobulare in situ (lobular carcinoma in situ)
CT	computerized tomography, ~ tomogram
CTV	clinical target volume
DBT	breast tomosynthesis
DCIS	ductal carcinoma in situ
DEGUM	Deutsche Gesellschaft für Ultraschall in der Medizin (German Society for Ultrasound in Medicine)
DGS	Deutsche Gesellschaft für Senologie (German Society of Senology)
DIEP flap	deep inferior epigastric perforator flap
DIN	ductal intraepithelial neoplasia
DIN	Deutsches Institut für Normung (German Institute for Standardization)
DKG	Deutsche Krebsgesellschaft (German Cancer Society)
DNA	deoxyribonucleic acid
EBCTCG	Early Breast Cancer Trialists' Collaborative Group
eDQE	effective detective quantum efficiency
EIC	extensive intraductal components
EMA	epithelial membrane antigen
EORTC	European Organization for the Research and Treatment of Cancer
ER	estrogen receptor
EUSOMA	European Society of Mastology
FEA	flat epithelial atypia
FSH	follicle-stimulating hormone
GCDFP	gross cystic disease fluid protein
Gd-DTPA	gadopentetate-dimeglumine
GnRH	gonadotropin-releasing hormone
GRE	gradient echo
HER	human epidermal growth factor receptor
HPF	high power field: field of vision on enlargement
HRT	hormone replacement theapry
IBCSG	International Breast Cancer Study Group
IC	infraclavicular
IDC	invasive ductal carcinoma
IGAP flap	inferior gluteal artery perforator flap
ILC	invasive lobular carcinoma
IPC	invasive papillary carcinoma
IR	inversion recovery
ISO	International Organization for Standardization
Ki-67	proliferation index
LCIS	lobular carcinoma in situ
LH	luteinizing hormone
LIN	lobular intraepithelial neoplasia
LM projection	lateromedial projection with medially applied detector
LVEF	left ventricular ejection fraction
MLO projection	mediolateral oblique projection
ML projection	mediolateral projection with laterally applied detector
MRM	modified radical mastectomy
MRM density	magnetic resonance mammographic density
MRI	magnetic resonance imaging
MRS	magnetic resonance spectroscopy
MQRA	Mammography Quality Standards Reauthorization Act
mTOR kinase	Mammalian target of rapamycin kinase
NHSBSP	National Health Service Breast Screening Program
NOS	not otherwise specified
NSABP	National Surgical Adjuvant Breast and Bowel Project
NST	no special type
PAS	publicly available specification
PAS stain	periodic acid–Schiff stain
PASH	pseudoangiomatous stromal hyperplasia
pCR	pathologically confirmed complete remission pathological complete remission pathological complete response
PGMI quality rating	perfect/good/moderate/inadequate (mammogram quality scoring system)
PgR	progesterone receptor
PIC	predominant intraductal components
PTV	planning target volume
ROI	region of interest
SC	supraclavicular

SE	spin echo
SERM	selective estrogen receptor modulator
SGAP flap	superior gluteal artery perforator flap
SIC	small intraductal components
SISH	silver in-situ hybridization
SLN	sentinel lymph node
SLNB	sentinel lymph node biopsy
SMA	smooth-muscle actin
T1W	T1-weighted
T2W	T2-weighted
TDLU	terminal duct lobular unit
TE	echo time
TGC	time gain compensation
TIC	time–signal intensity curve
TR	repetition time
TRAM flap	transverse rectus abdominis-musculocutaneus flap
TSE	turbo spin echo
UDH	usual ductal hyperplasia
UICC	Union for International Cancer Control/ Union internationale contre le cancer
VEGF	vascular endothelial growth factor
WHO	World Health Organization

Part 1

Anatomy, Physiology, and Pathology of the Breast

1 Development, Anatomy, and Physiology of the Mammary Gland

F. Baum

1.1 Development

Mammals (from the Latin *Mammalia*) are named for the fact that they feed their young on milk produced in the *mammary* gland. The various species of mammals have developed different numbers of mammary glands along the genetically determined milk line.

Mammalian breasts generally occur in pairs, as is the case in humans. Normally, humans have one breast on each side of the chest. At the prepubescent stage, both girls and boys have mammary buds. With the onset of puberty, the production of estrogen increases in the female body, causing changes in the mammary gland: the breast buds enlarge and the breast exhibits an increased build-up of adipose tissue. Milk is secreted in the mammary gland even when there is no pregnancy, but the volume of this basic secretion varies widely from one individual to the next, and often goes unnoticed.

1.2 Anatomy

The network of lactiferous ducts resembles a coral bush (▶ Fig. 1.1). From the point of exit at the nipple (mammilla), the milk ducts branch out within the breast, with a smaller duct diameter after each divergence. At the periphery, the smallest milk ducts originate from the lobules of the gland, where the milk is secreted. Some 30 of these milk ducts, leading from all four quadrants of the breast, open out into the mammilla and thus form the functional unit of the mammary gland.

The lobules are embedded in a network of connective tissue that permeates the breast, extending outward in an arc from somewhere in the deep fascia. Known as Cooper's ligaments, this tissue helps to provide structural integrity, supporting both lobules and adipose tissue. The ratio of fat to glandular tissue in the human breast varies widely between individuals, from almost 100% fat to almost 100% glandular tissue. In mammography, this is referred to as a lipomatous or an extremely dense parenchymal type, respectively.

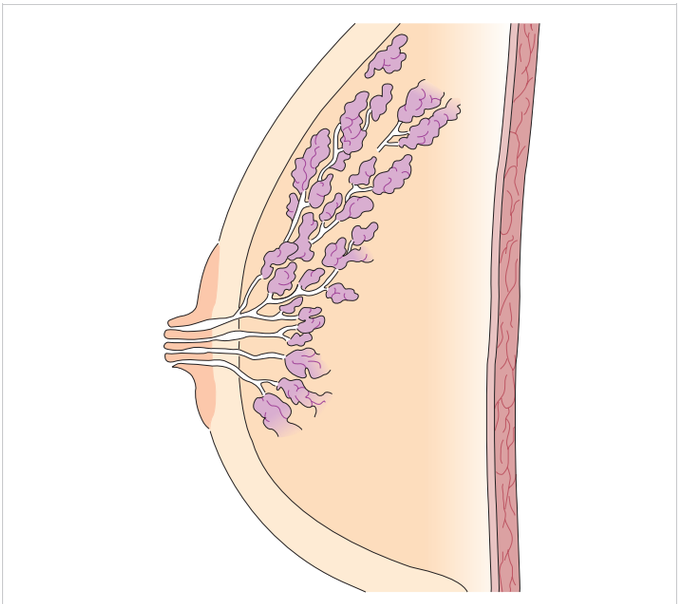

Fig. 1.1 The course of a milk duct. A mammary duct divides numerous times from the nipple. The smallest milk ducts originate from the lobules of the gland at the periphery and the milk is conducted from many lobules to the mammilla.

In addition to the secretory unit, made up of lobules and milk ducts, the mammary gland also contains lymph nodes that protect the body from bacterial incursion. Bacteria can enter through the milk duct openings at the nipple. The lymph nodes are commonly located in the upper outer quadrants, but have also been detected in the other three quadrants. Lymph flow is chiefly toward the underarm (axilla), first to the sentinel lymph node and from there to the other axillary lymph nodes. Only a very small portion enters the thoracic cavity via the parasternal lymph nodes. The arterial blood supply to the breast is carried mainly by the medial mammary branches of the internal thoracic artery (ca. 60%) and by the lateral mammary branches of the lateral thoracic artery (ca. 30%). Venous drainage is through the corresponding veins.

1.3 Physiology

The physiology of the mammary gland is controlled entirely by hormones. Metabolic activity in the mammary gland varies under the influence of estrogen. Even in childhood, hormonal fluctuations can occasionally cause swelling of the mammary bud. But this is usually a temporary phenomenon that reverts within a short time.

From the onset of menses, or menarche, many women observe changes in the mammary gland that recur every month. Following ovulation and approximately one week prior to menstruation, there is sometimes tenderness or a painful sensation of pressure in the breast, in some cases accompanied by swelling. These phenomena are triggered by the temporary gestagen production in the fallopian tubes, which usually abates when menstruation begins.

When pregnancy occurs and the fertilized egg implants in the uterine wall, the placenta begins producing chorionic gonadotropin. This stimulates the corpus luteum, which in turn triggers continuous secretion of progesterone, essential for maintaining the placenta in the uterus. The continuing production of progesterone during pregnancy also triggers further differentiation in the mammary gland and considerable growth of the milk-secreting lobules. The stimulation due to sucking, in the nursing phase, increases the secretion of the hormones prolactin and oxytocin by the pituitary gland. It is the interaction of these hormones which triggers the production of milk in the mammary gland, or lactation.

The effects of progesterone and prolactin on the mammary gland are reversible: the breast returns to its inactive state once breast feeding has ended. After weaning, the stimulation of the

mammary gland by prolactin and oxytocin is reduced, causing the gland lobules to become smaller and fewer. The changes in the breast that occurred with lactation are thus completely undone.

In menopause, the hormonal stimulation of the glandular tissue decreases considerably. Normally, there is also a reduction of glandular tissue in this phase, which increases the transparency of the mammary gland in mammography.

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2 Tumor Formation

F. Baum

2.1 Mutation, Carcinogenesis, and Angiogenesis

Life on earth is based on genes that are passed on from one generation to the next. Genetic material is transmitted in the form of nucleic acids (DNA) contained within the chromosome, which is in the nucleus of the cell. Each time a cell divides, it creates a complete copy of itself. Any errors that occur while the genetic information is being replicated are termed mutations. Considering the extensive amount of data contained within DNA, such errors are unavoidable. For the most part, these small mutations have no physiologically significant effect, but in some cases the resulting change is incompatible with the cell's life processes. In very rare cases, the mutation actually increases the new cell's chances of survival over those of the original cell. Throughout many millions of years and countless generations, this process has cumulatively led to a huge diversity of species.

Seen over the course of generations, mutation is what drives evolution—but in an individual it can endanger health and even life. A genetic mutation that changes the physiological properties of an organism may have any of a number of effects. If the modified cell continues to "play by the rules" of the organism then the mutation generally presents no danger.

If a cell loses its characteristic property of living within a community of cells, however, then it has become what we call a cancer cell. Generally, a series of six to eight mutations is required before this point is reached. Specifically, cancer cells lack the property of "contact inhibition," the trait that inhibits cell migration into other cells and organs (▶ Fig. 2.1). In a manner of speaking, contact inhibition is what regulates the different "territories" in multicellular organisms. It prevents cells from spreading into organs in which they do not belong.

The loss of contact inhibition makes it possible for a cancer cell to infiltrate foreign tissue. This process is aided by certain enzymes that dissolve connective tissue and other structures. Furthermore, cancer cells can leave their point of origin and move via lymph vessels and blood vessels. These processes are termed lymphatic spread and hematogenous spread, respectively, and can lead to the formation of metastases.

Cancer cells are characterized by an accelerated metabolism and an exceedingly rapid cell cycle. They thus have particularly high nutritional requirements. To meet their extensive needs, these cells secrete enzymes that stimulate the surrounding tissue to rapidly form a system of capillaries, a process termed angiogenesis or tumor angiogenesis. These new capillaries are morphologically simple endothelial tubes that lack the complex structure of normal blood vessels but suffice to enable the development of carcinoma cells and to supply them. This capillary network drains energy and nutrients from the surrounding organs, and consequently from the overall organism. Sometimes, however, cancer cells grow so rapidly that even the dedicated blood supply cannot feed all parts of the tumor, and cancer cells begin to die, usually in the center of the tumor.

2.2 Risk Factors

The probability that a woman will develop breast cancer at some point in her life depends on a number of different factors (▶ Table 2.1, ▶ Table 2.2). Oncogenes and tumor suppressor genes play an important role in the regulation of healthy cell growth and tumor development. Oncogenes accelerate cell growth, while tumor suppressor genes slow it down.

On average, a woman in Europe has an 11% chance of developing breast cancer. In industrialized countries, the incidence

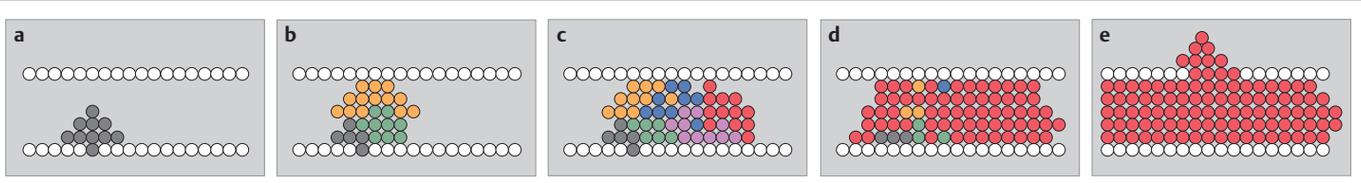

Fig. 2.1 Tumor development. (a) A mutated cell clone (gray) has evolved within a milk duct from the epithelium (white). **(b)** Over time, a second (green) and a third (orange) mutation occur. **(c)** Further mutations in the course of time; e.g., up to a sixth mutation (red). **(d)** This cell clone has lost its contact inhibition and thus supplants the surrounding cells. **(e)** With further time, the cell clone has penetrated the boundaries of anatomical structures: it has become an invasive tumor.

Table 2.1 Absolute breast cancer risk by age (from Royal New Zealand College of General Practitioners [RNZCGP]. Early detection of breast cancer 1999. Wellington, New Zealand: RNZCGP;1999:1–61)

Risk of disease	Age group (years)			
	25–44	45–54	55–79	>80
Absolute 5-year risk (%)	<0.5	0.5–1	1–1.5	1.5–2
Per 1,000 women	<5	5–10	10–15	15–20

Table 2.2 Relevant risk factors for developing breast cancer, in descending order of significance (from Deutsche Gesellschaft für Senologie e.V., Deutsche Krebshilfe e.V. S3-Leitlinie "Brustkrebs-Früherkennung in Deutschland". 1. Aktualisierung. München: W. Zuckschwerdt; 2008)

Risk factors	Relative risk
Cancer in childhood	20
Radiotherapy (age 9–15 years)	10
Mantle-field radiotherapy	10
High-risk	4.0–10
Type ACR IV tissue density	3.8–5.2
Status post surgery for contralateral carcinoma:	
• Age < 45 years	5.0–9.0
• Age 45–59 years	3.7–4.1
• Age ≥ 60 years	1.8–3.0
Status post surgery for DCIS (premenopause)	5
Status post surgery for ADH	2.0–4.0
Menarche at age < 11 years	3
Menopause at age > 54 years	2

Abbreviations: ACR, American College of Radiology; ADH, atypical ductal hyperplasia; DCIS, ductal carcinoma in situ.

of breast cancer is rising and the average age of initial illness is dropping. In Asia and Africa, this risk is significantly lower, which suggests that certain lifestyle factors may play a significant role. In those parts of China, for example, where Western standards of living have been introduced, the incidence of breast cancer is increasing accordingly. One possible explanation for this is the decreased bodily production of melatonin as a result of the use of artificial light, which shortens the night phase. This results in an increased risk of breast cancer. A lower risk of breast cancer is seen among women who have late menarche or early menopause, and among those who bear and breast-feed children. The risk is increased, on the other hand, by such factors as obesity, alcohol consumption, and lack of physical exercise. Female hormone replacement therapy—in particular if hormones are taken for long periods—increases the risk of breast cancer 1.5-to 3-fold.

Take Home Points

- **Age and breast cancer risk:** The most important population-based risk factor for breast cancer is increasing age.
- **Mammographic density and breast cancer risk:** A high mammographic density (ACR III or IV) is one of the greatest individual risk factors.

2.3 Genetic Risk Factors

In addition to lifestyle-related factors, genetic factors can also affect a woman's risk of breast cancer. In families with a high incidence of breast cancer, an individual's lifetime risk of developing breast cancer can be as high as 80%. In these families there is also an increased incidence of ovarian carcinoma.

Table 2.3 High-risk genes with known germline mutations and associated lifetime risk of breast or ovarian carcinoma

Gene	Percent lifetime risk of	
	Breast carcinoma	Ovarian carcinoma
BRCA1 (detectable)	80	45
BRCA2 (detectable)	80	20
BRCA3 (detectable)	?	?
BRCA4	?	?

The high incidence of these cancers in high-risk families is due to defects in repair enzymes, which play an important role in cell division in both organs. These enzymes are proteins that check and correct the double-stranded DNA during the cell division process, normally reducing the number of mutations. If the genes coding for these repair enzymes are altered, then these enzymes can lose either the ability to detect replication errors or the ability to correct detected replication errors. These defective enzyme genes are called breast cancer (or *BRCA*) genes (▶ Table 2.3). Other genes associated with breast/ovarian cancer are *RAD51C* and *RAD51D*. It has also long been known that persons who have ataxia telangiectasia or Li–Fraumeni syndrome have a higher risk of breast cancer.

BRCA mutations are inherited in an autosomal dominant inheritance pattern: they can be inherited from father or mother. If one parent carries this mutated gene, each child has a 50% chance of inheriting it.

Note

It can be assumed that some 5 to 10% of all women who have breast carcinoma have an autosomal dominant genetic predisposition.

The presence of an autosomal dominant inheritable germline mutation with a probability of more than 10% may be assumed if one of the following constellations exists within the family:

- At least three women with breast cancer, regardless of age.
- At least two women with breast cancer, one of them before age 50 years.
- At least two women with ovarian cancer.
- At least one woman with breast cancer and one woman with ovarian cancer.
- At least one woman with both breast cancer and ovarian cancer.
- At least one woman with breast cancer diagnosed before age 36 years.
- At least one woman with bilateral breast cancer diagnosed before age 51 years.
- At least one man with breast cancer and one woman with breast or ovarian cancer.

Some cancer societies see a high-risk constellation in families in which women develop breast or ovarian cancer at an early age:

- Two women with breast and/or ovarian cancer diagnosed before age 50 years.

- One woman with unilateral breast cancer diagnosed before age 30 years.
- One woman with bilateral breast cancer diagnosed before age 40 years.
- One woman with ovarian cancer diagnosed before age 40 years.

Consultation at a specialized and interdisciplinary facility is recommended for individuals from families with a potentially high-risk constellation. These facilities provide counseling and can check whether the inclusion criteria indicate that genetic testing is advisable.

2.4 Prevention

2.4.1 Primary Prevention

Primary prevention refers to the prevention of the development of disease in the first place. The removal of benign polyps during a colonoscopy can, for example, prevent the development of malignant colorectal tumors. In the case of breast cancer, primary prevention consists in removing both breasts (bilateral mastectomy).

2.4.2 Secondary Prevention

The aim of secondary prevention is to detect the disease in the earliest possible stage. The three imaging modalities most commonly used for the detection of breast cancer are mammography, ultrasound, and magnetic resonance imaging (MRI). The aim of using these procedures is to detect changes in the breast that are characteristic of carcinomas. Each method has its own particular strengths and the detectability of alteration in tissues depends on factors such as the size of a tumor and, in particular, the ability to distinguish tissue with breast cancer changes from the surrounding normal structures.

The standard method used in early detection of breast cancer is X-ray mammography: the *breast radiograph*. The sensitivity of mammography is approximately 70%, with a specificity (i.e., accuracy) of about 90%. The same figures are obtained with breast ultrasonography for the early detection of breast carcinomas. However, both methods show considerably lower values for both sensitivity and specificity in detecting tumors of 5 to 10 mm diameter. The most reliable technique for the early detection of breast carcinoma is MRI of the breast. Available study data indicate that both the sensitivity and the specificity of this examination are greater than 90%. This also applies for tumors between 5 and 10 mm in size, but only when stringent quality control standards are applied.

Early-detection diagnostics are not the same as a diagnostic work-up. The latter is applied when symptoms such as pain, palpable lumps, retractions, discoloration, or bleeding are reported.

Note

The objective of early-detection diagnostics is to detect tumors before clinical changes have occurred.

2.4.3 Tertiary Prevention

Tertiary prevention consists in minimizing complications and recurrences once cancer has developed.

2.5 Epidemiology, Incidence, and Mortality

Breast carcinoma is the most common cancer in women in Western societies. Approximately one woman in nine will have breast cancer at some point in her life. This ratio includes a large number of women with a normal lifetime risk (6–8%) and a somewhat lower number of women who have an individual high-risk profile (lifetime risk ca. 80%).

Some 72,000 new cases of breast carcinoma are diagnosed each year in Germany. In many other regions around the world, the risk is much lower. The incidence of a disease is defined as the number of new cases diagnosed per 100,000 women per year. In Germany, breast carcinoma incidence is about 120 per 100,000 women per year.

Breast cancer also has the highest mortality rate for women, accounting for some 17.3% of cancer deaths among women. The mortality rate is defined as the number of deaths caused per 100,000 women per year. In Germany, the mortality rate for breast cancer is about 40 per 100,000 per year. Some 17,000 patients per year die in Germany as a result of breast cancer (▶ Fig. 2.2, ▶ Fig. 2.3).

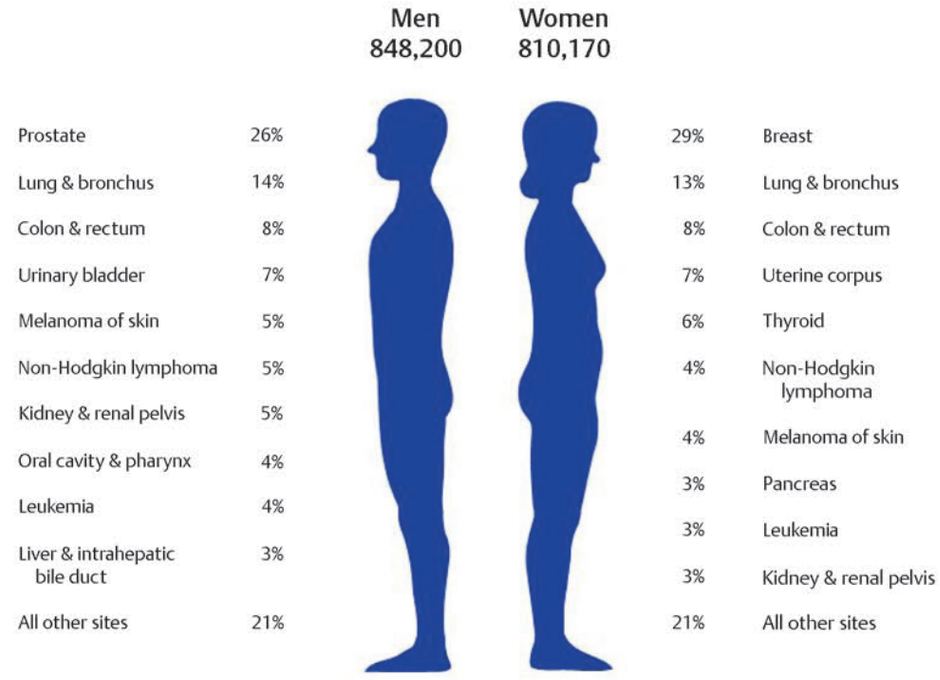

Fig. 2.2 Relative percentages of the most common tumor locations among all new cancer cases in men and women in the USA in 2015 (from American Cancer Society https://www.cancer.org/search.html?q=Cancer%20Fact%20and%20Statistics%202011).

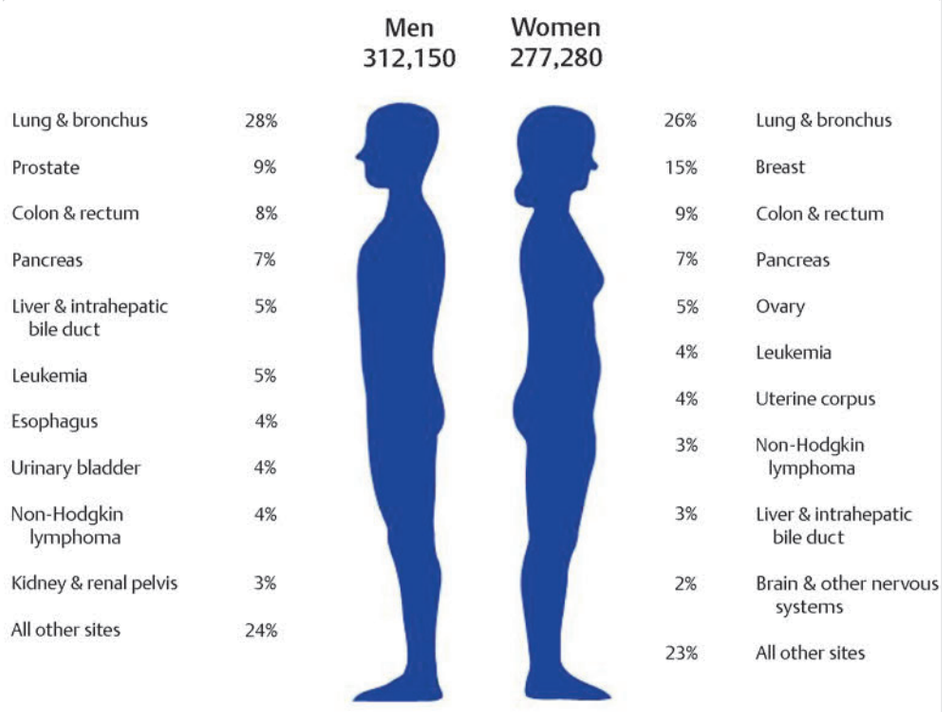

Fig. 2.3 Relative percentages of the most common tumor locations among all cancer deaths in men and women in the USA in 2015 (American Cancer Society https://www.cancer.org/search.html?q=Cancer%20Fact%20and%20Statistics%202011).

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3 Pathology of Benign and Malignant Changes in the Breast

J. Rueschoff

3.1 Benign Changes

3.1.1 Histological Principles

The breast is made up of 15 to 25 glands (lobules or segments) (▶ Fig. 3.1a). These glands comprise a dense system of bifurcating ducts and ductules ending in the milk-secreting lobules (acini; ▶ Fig. 3.1b). The large majority of breast diseases originate in the epithelial cells that line the ducts and lobules. The most frequent point of origin is at the ends of the glandular "tree," the terminal duct lobular unit (TDLU) (▶ Fig. 3.1c, d).

Immunhistochemically, the luminal cell layer (both glandular and ductal) and the basal myoepithelial cell layer develop from a progenitor cell expressing basal (high molecular weight) cytokeratins (CK5/6 or CK5/14). The mature myoepithelial cell may revert to being CK5/6 negative, though myofilaments with antibodies for smooth muscle actin (SMA) and CD10[32] can be detected. Mature luminal duct and gland cells are positive for the low molecular weight cytokeratin CK8/18, but negative for CK5/6 (progenitor cell model[1,7]).

3.1.2 Nonneoplastic, Nonproliferative Diseases of the Breast

Diseases of the breast are among the most common disorders of organs in women and are often associated with the formation of a palpable lump. In principle breast diseases can also develop in men. It is important to distinguish between palpable lumps caused by true new tissue growth (tumor or neoplasia) and those that do not exhibit uncontrolled, progressive growth (nonneoplastic, pseudotumorous). Because breast tissue is hormone-responsive, changes occur particularly during the menstrual cycle but also during pregnancy and lactation, which can sometimes promote changes such as the formation of cysts (mastopathy), or inflammatory processes (mastitis). In individual cases it can be difficult, not only clinically and in breast imaging, but also pathologically, to distinguish nonneoplastic benign changes from neoplastic malignant lesions. Indeed, a reliable evaluation of pathological findings in the breast can be a challenge even for pathologists. In the following subsections, the typically diffuse changes in breast tissue are described and distinguished from those lesions that typically lead to tumor formation.

Defects and Supernumerary Structures

Congenital abnormalities of the breast are relatively rare and are divided into defects and supernumerary structures:

- Defects: These range from the complete absence of breast tissue and nipple (amastia) to isolated abnormalities of the nipple (athelia, microthelia) or the breast (amatia, aplasia) and to bilateral or unilateral underdevelopment of the breast (micromastia, anisomastia).

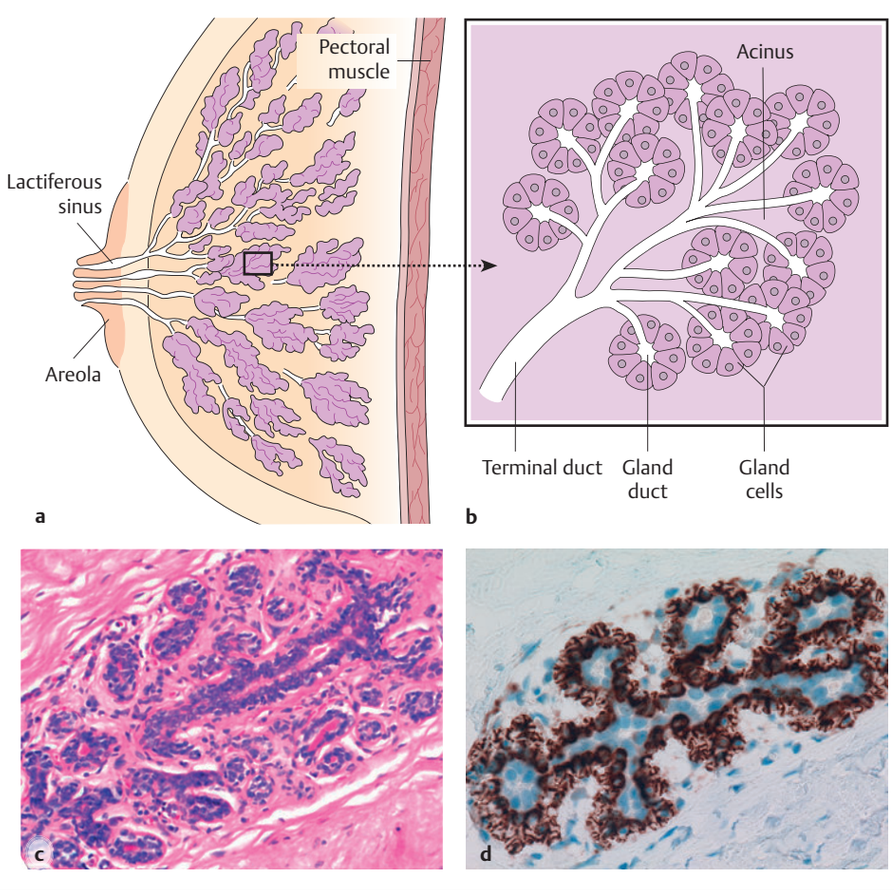

Fig. 3.1 Anatomy of the breast. (a, b) Schematic diagrams. **(c, d)** histology and immunohistology. **(a)** Mammary gland with ca. 15 to 25 individual lobes, each ending at the nipple orifice. **(b)** Detail from **(a)**: The branching ducts lead into terminal ducts (ductules) and end in the secretory lobes (acini). **(c)** Terminal duct lobular unit (TDLU). **(d)** TDLU with a luminal (blue nuclei) and a basal myoepithelial cell layer (brown represents CD10).

- Supernumerary structures: Supernumerary nipples (polythelia) and/or breasts (polymastia) develop in the milk line and are found in approximately 3% of the population, with no gender preference. The most common localizations of such formations are in the axilla (45% of cases), near the breast (25%), and in the medioclavicular line of the chest wall (12%). Carcinomas in a mamma aberrata (dystopic carcinomas) are rare and are prognostically unfavorable.[40]

Macromastia

The term "macromastia" (diffuse hypertrophy of the breast) refers both to premature (infantile) breast development and to excessive growth of the breast beyond what is age-appropriate. Macromastia occurs most frequently in adolescence, with proliferation of ductal epithelia and fibrosis of breast tissue being the most prominent histological features. Most commonly there is an increase in fatty tissue (lipomatous macromastia). In the differential diagnosis, the following secondary forms must be distinguished from primary macromastia:

- Paraneoplastic: in the case of endocrine-active tumors (hypophyseal adenoma, small-cell bronchial carcinoma, Cushing's disease, acromegaly, dysgerminoma).
- Drug related (digitalis).
- Tumor-related: by infiltration of the breast tissue (malignant lymphomas).

Fibrocystic Mastopathy

Characteristic features of a simple fibrocystic breast condition are morphological changes in which fibrosis of the mammary tissue with duct ectasia is predominant but not epithelial proliferation. Such changes can be detected in ca. 50% of women age 30 years and over and are considered by some authors to be a variant of the norm with no pathological significance. There is no associated increased risk of breast cancer.[1]

Typical histological findings include the following changes:

- Cysts and duct ectasia: The lactiferous ducts are noticeably enlarged but generally show an intact epithelial lining (▶ Fig. 3.2), although solitary cysts (larger than 1 cm) may form.
- Fibrosis: This is an intralobular or perilobular collagen fiber proliferation in the breast stroma.
- Metaplasia: This is usually an apocrine metaplasia with cylindrical, red eosin-stained epithelia (similar to sweat glands).

Mastitis

Inflammations of the breast are either acute (usually bacterial infection) or mainly chronic (usually resulting from retention of secretion). Reactive specific and granulomatous inflammatory changes are rare.[2]

Acute Mastitis

Acute inflammations (thelitis, areolitis) are usually caused by contact infection during breastfeeding and can lead to a canalicular transmission of the inflammation to the glandular tissue (puerperal mastitis). The most frequent pathogen (95% of cases) is *Staphylococcus aureus* from the nasopharyngeal cavity of the child, the mother, or the nursing staff. Purulent inflammations of the mammary gland (nonpuerperal mastitis) are rare after the postnatal period. These develop due to displacement of the lactiferous duct by nipple calluses, scars, or tumors with subsequent retention of secretions. Secondary colonization can then lead to formation of a suppurating abscess. Histologically, there is a leukocytic infiltration of the milk ducts and lobules with invasion of the mantle and supporting tissue. Healing of abscesses and fistulas can leave scarring and deformation of the breast.

Chronic Periductal Mastitis (Retention Syndrome)

About one-third of nonpuerperal mastitis cases are nonbacterial, chemically induced inflammations caused by intraductal secretion retention (▶ Fig. 3.3a). Histological features include ectatic

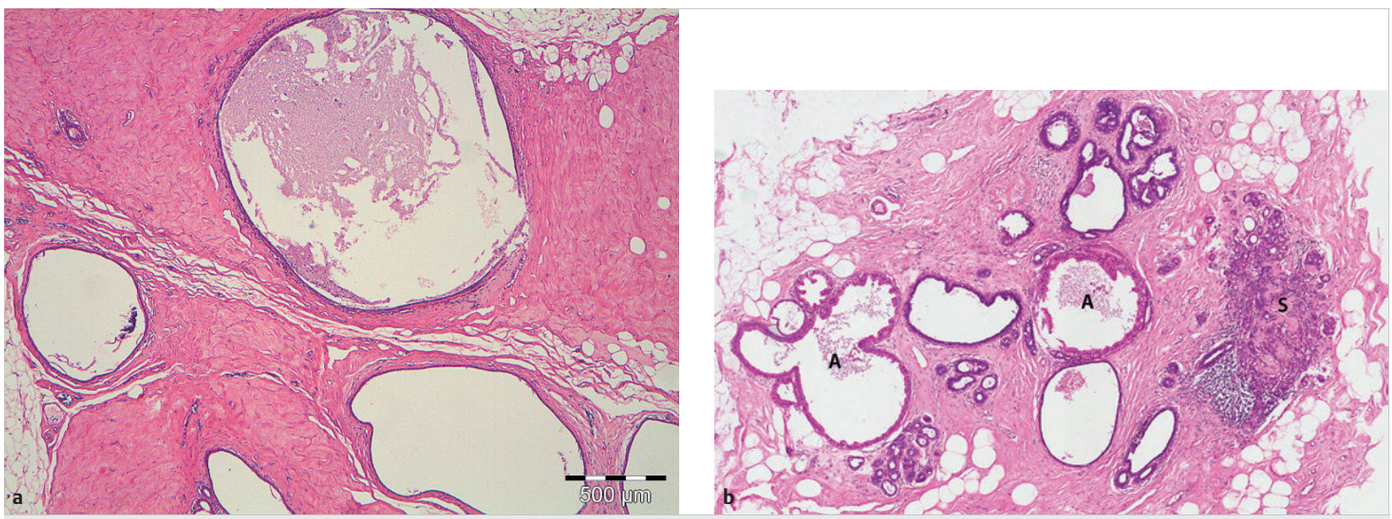

Fig. 3.2 Fibrocystic mastopathy. (a) Cystic duct ectasia. **(b)** Fibrocystic tissue transformation with ectatic ductules, partly lined by (reddish) apocrine metaplastic epithelium (A), and incipient focal lobule sclerosis (S). (From Bock K, Ramaswamy A, Köhler H. Fortbildungskurs zur Aufrechterhaltung und Weiterentwicklung der fachlichen Befähigung für Pathologen [6.10.2012]—Referenzzentrum Mammographie Südwest am Universitätsklinikum Gießen-Marburg am Standort Marburg [Course text].)