Pathology of the breast and pregnancy

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• Normal structure and function
• Clinical features of breast lesions
• Diagnostic methods
• Inflammatory conditions
• Proliferative conditions
• Benign tumors
• Breast carcinoma
• Other tumors
**Lobules**

The lobules are the secretory units of the breast. Each lobule consists of a variable number of acini, or glands, embedded within loose connective tissue and connecting to the intralobular duct. Each acinus is composed of two types of cells, epithelial and myoepithelial.
Development of the breast requires the coordinated action of many hormones. The precise role of each hormone is difficult to determine since they may have both growth and secretory effects, and may regulate the activity of each other.

Fig. 16.1
The action of hormones in the development of the breast
Some hormones have a definite effect (→), whereas the role of others is less certain (←).
**Clinical features**

Most pathological lesions of the breast present as a lump or lumps. These can vary in their nature depending on their cause: well-circumscribed or ill-defined; single or multiple small nodules; soft or firm; mobile or attached to skin or underlying muscle. These features assist in the clinical distinction between breast lesions and breast carcinomas, but they are relatively weak discriminators on their own.

<table>
<thead>
<tr>
<th>Clinical presentation</th>
<th>&lt;25 years</th>
<th>25–35 years</th>
<th>35–55 years</th>
<th>&gt;55 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mobile lump</td>
<td>Fibroadenoma</td>
<td>Fibroadenoma</td>
<td>Fibroadenoma</td>
<td>Phyllodes tumour</td>
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<tr>
<td>Ill-defined lump or lumpy areas</td>
<td>Uncommon</td>
<td>Fibroadenosis</td>
<td>Sclerosing adenosis</td>
<td>Fibrocystic change</td>
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<tr>
<td>Firm lump ± tethering</td>
<td>Uncommon</td>
<td>Carcinoma*</td>
<td>Carcinoma</td>
<td>Carcinoma</td>
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<tr>
<td>Nipple discharge</td>
<td>Uncommon</td>
<td>Uncommon</td>
<td>Duct ectasia</td>
<td>Duct ectasia</td>
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<tr>
<td>Clear</td>
<td>Uncommon</td>
<td>Uncommon</td>
<td>Duct papilloma</td>
<td>Duct papilloma</td>
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<tr>
<td>Bloody</td>
<td>Nipple adenoma</td>
<td>Uncommon</td>
<td>Paget’s disease</td>
<td>Paget’s disease</td>
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<tr>
<td>Nipple ulceration, eczema</td>
<td>Nipple adenoma</td>
<td>Nipple adenoma</td>
<td>Nipple adenoma</td>
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</tbody>
</table>

*Carcinoma is unusual in this age group, but can occur.*
Diagnostic methods

• Fine needle aspiration cytology
• True-Cut biopsy
• Examination of frozen section
• Mammography

Fine needle aspiration cytology

This technique is increasingly employed. When a woman presents at a clinic with a breast lump, a needle can be inserted into the area and cells aspirated without the need for even a local anaesthetic. After smearing and staining, the cells are examined by a pathologist, and if the specimen is adequate a diagnosis can be made.
Mammography

X-raying of the breasts is used to help in the diagnosis of both palpable and impalpable lesions. This technique is the basis of screening programmes, which try to detect impalpable small breast cancers, i.e. ‘early’ tumours. Lesions detected in this way require an X-ray-directed guidewire to be inserted into them before surgery to help the surgeon find the right area. It is important that the pathologist carefully examines the tissue to ensure that the lesion has been removed.
**Tru-Cut biopsy**

Another approach which can be used in the clinic is Tru-Cut biopsy, in which a core of tissue is removed using a biopsy needle.

**Examination of frozen section**

A further approach is that of examining the breast lesion very rapidly by frozen section at the time of surgery. A small sample is frozen, and sections are cut, stained and interpreted by a pathologist within a few minutes.
**Inflammatory conditions**

- Infections of the breast are uncommon, usually complications of lactation
- Duct ectasia can cause nipple discharge, commoner in older women
- Fat necrosis is due to trauma, more frequent in the obese

**Duct ectasia**

The aetiology is unknown. The ducts are dilated and filled with white-green viscid matter; this material may be discharged from the nipple. The tissue around the ducts contains lymphocytes, plasma cells, and macrophages, with a significant degree of fibrosis.

Trauma is thought to be the cause of **fat necrosis**, although a history is not always obtained. It usually presents as a discrete lump and can therefore mimic a carcinoma clinically.
**Proliferative conditions**

- Increase in frequency towards menopause, then rapid decrease
- Present as diffuse granularity, ill-defined lump or discrete swelling
- Variety of histological changes
- Adenosis commoner in younger age group, cysts commoner nearer the menopause
- Women with atypical hyperplasia are at increased risk of developing breast cancer
- Gynaecomastia is enlargement of breasts in men
The commonest proliferative condition of the breast is **fibrocystic change**. Although benign and non-neoplastic, it is important because:

- In many women, it causes severe periodic discomfort
- One component, epithelial hyperplasia, is associated with an increased breast cancer risk
- It causes palpable lumps mimicking breast cancer

The gross appearance of the breast tissue shows variation from case to case. In younger women, it is more common to find nodules of soft pink or grey tissue, up to 3 mm in diameter, which represent areas of epithelial proliferation, whereas in women nearer the menopause cysts are frequently seen. These cysts can vary in size from 2 to 20 mm and, rarely, a solitary large cyst can be seen. The small cysts are often multiple.

This is the gross appearance of fibrocystic changes in the breast. A 1.5 cm cyst is noted here. This can lead to palpation of an ill-defined "lump" in the breast. Sometimes, fibrocystic changes produce a more diffusely lumpy breast.
The relative imbalance between oestrogen and progesterone in each menstrual cycle could be an important etiological factor.

Cystic change is considered to be due to an imbalance between hyperplasia of ductal and lobular epithelium, together with dilatation, that occur with each menstrual cycle, and subsequent regressive changes. The cystic dilatation thus occurs because of a distortion of cyclical changes rather than as a consequence of obstruction, which is the usual cause in other organs.
**Histology**

- Sclerosing adenosis
- Epithelial hyperplasia
- Papillomatosis
- Cysts
- Apocrin metaplasia
- Adenosis
- Fibrosis

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**Adenosis**

Adenosis is enlargement of the lobules which contain many, up to hundreds, of acini.
**Sclerosing adenosis**

In sclerosing adenosis there is lobular proliferation but the acini become distorted.

**Epithelial hyperplasia**

Epithelial hyperplasia, previously called epitheliosis, is the proliferation of epithelial cells.

**Papillomatosis**

Papillomatosis takes the form of simple papillary processes projecting into the lumens of dilated ducts or small cysts.
Cysts

Cysts develop through dilatation of the acini of the lobules and the terminal ducts. These cysts may remain small, or enlarge to sizes up to 20-30 mm.

Atypical hyperplasia

The epithelial hyperplasia that can result in total or partial occlusion of the acini and small ducts, disordered orientation of cells, nuclear pleomorphism and occasional mitotic figures.

If the biopsy contains areas of atypical hyperplasia, the woman has a risk of developing cancer 5 times higher than that of a woman with non-proliferative lesions, and the risk increases if there is a family history of breast cancer. Cysts alone do not appear to increase the risk.
Gynaecomastia is benign enlargement of the male breast tissue. The breast may resemble that of a young adolescent female in appearance and consistency, or there may be a firm, mobile disc beneath the nipple. The condition is unilateral in 75% of cases. The ducts are dilated and there is a variable degree of epithelial proliferation.
**Benign tumors**

- Fibroadenomas
- Duct papillomas
- Adenomas
- Connective tissue tumors

**Fibroadenoma**

- Commonest type of benign tumour, mainly in young women
- Arises from connective tissue and epithelium
- Clinically, mobile on palpation

Fibroadenomas are well circumscribed with a lobulated appearance, and range in size from 10-40 mm in diameter although larger tumors can occur in juvenile fibroadenoma.
The greatest incidence of fibroadenomas is in the third decade, although they can occur at any time from puberty onwards. The tumors are usually solitary, although some women do develop multiple fibroadenomas.

The pericanalicular type is characterised by numerous small, rounded, duct-like structures around which the connective tissue is concentrically arranged. The ductular structures curving over and between the overgrown connective tissue masses (intracan.).
**Duct papilloma**

- Less common, occur in middle-aged women
- Presents as blood-stained nipple discharge
- Usually solitary lesion, occurring in large ducts
- Papillary structures, with fibrovascular core covered by benign epithelium

Duct papillomas consist of branching fibrovascular cores covered by epithelium, which is cytologically benign.
**Adenomas**

- Rare, arise only from epithelium
- Tubular and lactating adenomas occur in young women
- Nipple adenomas occur at all ages; there is a mass beneath the nipple which can ulcerate the skin
Breast carcinoma

- 20% of all cancers in women
- Commonest cause of death in women in 35-55 age group

Risk factors

The risk factors identified to date are:

• Female sex; risk increases with age
• Long interval between menarche and menopause
• Age at first full-term pregnancy
• Obesity and high-fat diet
• Family history of breast cancer
• Geographic factors
• Atypical hyperplasia in previous breast biopsy
Aetiological mechanisms

- Overexposure to oestrogens and underexposure to progesterone important
- No definite relationship to oral contraceptives
- Some tumors contain receptors for estrogen and progesterone and respond to hormone manipulation
- No good evidence for viral involvement

Estrogen receptors can be detected in varying amounts in about 70% of breast cancers. The progesterone receptor is present in about 35% of tumors, and many of the women whose tumors contain both types of receptors are more likely to respond to some form of hormone manipulation therapy. This suggests that hormones are important in the growth and maintenance of these carcinomas.
**In situ carcinomas, DCIS, LCIS**

- Tumour is confined to ducts (intraduct)(DCIS) or acini (intralobular)(LCIS)

- Intraduct carcinoma is unilateral, in pre- and post-menopausal women, and has several forms

- Intralobular carcinoma occurs in pre-menopausal women, has no clinical features, is often bilateral, and can be multifocal

It can present as a palpable mass, especially if extensive and associated with fibrosis. If the larger ducts are involved, presentation can be as a nipple discharge, or as Paget’s disease of the nipple. The disease can be found incidentally in surgical biopsies or detected by mammography screening. Pure intraduct carcinoma accounts for about 5% of breast carcinomas which present clinically.
The macroscopic appearances depend on the type of *intraduct carcinoma*. If it is comedo carcinoma, creamy necrotic material exudes from the cut surface of the breast, rather similar in appearance to comedones. Other types have less characteristic appearances.
**Invasive carcinomas**

- Occur in pre- and post-menopausal women
- Most are infiltrating duct type
- Infiltrating lobular carcinomas can be multifocal
- Less common types include mucinous, medullary, papillary and tubular carcinomas

An ‘invasive’ tumour is one whose cells have broken through the basement membrane around the breast structure in which they have arisen, and spread into the surrounding tissue.
The *histological types* of infiltrating carcinoma and their relative incidence for palpable tumours are:

- Invasive (NOS); ductal (85%)
- Invasive lobular (10%)
- Mucinous (2%)
- Tubular (2%)
- Medullary (< 1%)
- Papillary (< 1%)
- Others (< 1%)

Carcinomas vary in size from less than 10 mm in diameter to over 80 mm, but are often 20-30 mm at presentation. Clinically, they are firm on palpation and may show evidence of tethering to the overlying skin or underlying muscle. The skin also shows “orange skin”, dimpling due to lymphatic permeation. The nipple may be retracted due to tethering and contraction of the intramammary ligaments.
Gross features

The macroscopic appearance of the tumors tends to depend on the amount or type of stroma within the carcinoma. It is this which gave rise to the terms previously applied to tumors: **scirrhous, medullary (or encephaloid) and mucinous (or colloid)**.

The term scirrhous implies that there is a prominent fibrous tissue reaction, usually in the central part of the tumor. This results in the carcinoma having a dense white appearance, which grates when cut. Yellow streaks may be seen, and these are due to the presence of elastic tissue within the tumor. Carcinomas with a prominent stromal reaction usually have **irregular edges**, extending into the adjacent fat or breast parenchyma.

Medullary or encephaloid (brain-like) tumors are very cellular with little stroma. The edges of the carcinoma are **often more rounded** and discrete than those of the scirrhous tumors. Necrosis is common. When palpated the tumors feel much softer.

Mucinous and colloid carcinomas have a predominance of mucin, or jelly-like, material within them. They usually have a **well-defined edge**.
Here is a side by side comparison of the gross characteristics of a classic infiltrating ductal carcinoma on the left and a benign fibroadenoma on the right.
Infiltrating ductal carcinoma

Histologically, the tumour cells are arranged in groups, cords and gland-like structures. Quite marked variations can be seen between different carcinomas even though they are of the same type.

The amount of stroma between the tumour cells can also vary, but in those carcinomas in which it is prominent it is most marked at the centre, with the periphery being more cellular. Collections of elastic tissue (elastosis) around ducts or within the stroma are common in tumours with a scirrhoues reaction.
The degree of differentiation of the tumour is based on the extent to which it resembles non-tumorous breast: whether the cells are in a gland-like pattern or as solid sheets; the degree of nuclear pleomorphism; and the number of mitotic figures present. A well-differentiated infiltrating duct carcinoma tends to behave less aggressively than a poorly-differentiated tumour, which is composed of sheets of pleomorphic cells with large numbers of mitotic figures.
**Infiltrating lobular carcinomas** have abundant fibrous stroma, so that macroscopically they are always scirrhus. While infiltrating ductal carcinomas usually form at one focus in the breast, infiltrating lobular carcinomas can be multifocal throughout the breast.

**Histologically** the cells are small and uniform and are dispersed singly, or in columns one cell wide (‘Indian files’), in a dense stroma. Elastosis can be present. The cells infiltrate around pre-existing breast ducts and acini, rather than destroying them as occurs with infiltrating duct carcinomas.
**Mucinous carcinomas**

Mucinous carcinomas (also known as colloid, mucoid and gelatinous carcinomas) usually arise in post-menopausal women and comprise 2-3% of infiltrating carcinomas.

Macroscopically, the tumors are well circumscribed and have a soft, grey, gelatinous cut surface. They vary in size from 10-50 mm in diameter.

These carcinomas comprise small nests and cords of tumour cells, which show little pleomorphism, embedded in large amounts of mucin.

The survival of women with mucinous carcinomas is better than those having infiltrating duct or lobular carcinomas.
Tubular carcinomas

As the name implies, tubular carcinomas are well-differentiated carcinomas composed of cells arranged as tubules. They are usually small lesions, less than 10 mm in diameter, and are firm, gritty tumours with irregular outlines.

Histologically, they are composed of well-formed tubular structures, the cells of which show little pleomorphism or mitotic activity. The stroma is dense, often with elastosis.

Patients with tubular carcinomas do extremly well-better than those with well-differentiated infiltrating duct carcinomas.
Medullary carcinoma

Medullary carcinomas are circumscribed and often large with areas of necrosis. Histologically, they are composed of large tracts of confluent cells with little stroma in between them. The cells show quite marked nuclear pleomorphism, and mitotic figures are frequent. There is never evidence of gland formation. These cytological appearances put them into the ‘poorly differentiated’ category. Around the island of tumour cells there is a prominent lymphocytic infiltrate, predominantly T-lymphocytes, with macrophages.

Despite the aggressive cytological features of these tumours, the patients have a significantly better 10-year survival than women with infiltrating duct carcinomas. It may be that the lymphocytic and macrophage infiltrate has a beneficial effect.
Papillary carcinoma

Papillary carcinomas are rare tumours, which occur in post-menopausal women. They are usually circumscribed and can be focally necrotic, with little stromal reaction. The tumours are in the form of papillary structures, and areas of intraductal papillary growths are usually found.

The prognosis of these carcinomas is probably better than the much more common infiltrating duct carcinoma.
**Prognostic factors**

- These can be gross and histological features - type, grade, size

- Spread, local to lymph nodes or distant

- Behavioural characteristics of carcinomas, such as growth rates and hormone receptor status, Her-2 overexpression, DNA content

Herceptin and anti-estrogen treatment!
Stratification by immunohistochemistry and genetics

Luminal A type: ER+, PR+ and HER2 -. The gene expression patterns of these cancers are similar to normal cells that line the breast ducts and glands (the inside of a duct or gland is called its lumen). Luminal A cancers are low grade, tend to grow fairly slowly, and have the best prognosis.

Luminal B type: ER+, PR+ and HER2 +. Luminal B cancers generally grow somewhat faster than luminal A cancers and their outlook is not as good.

HER2 type: These cancers have extra copies of the HER2 gene (HER2+) and sometimes some others. They usually have a high-grade appearance under the microscope. These cancers tend to grow more quickly and have a worse prognosis, although they often can be treated successfully with targeted therapies aimed at HER2 which are often given along with chemotherapy. ER and PR are negative.

Basal type: Most of these cancers are of the so-called triple-negative type, that is, they lack estrogen or progesterone receptors and have normal amounts of HER2. The gene expression patterns of these cancers are similar to cells in the deeper basal layers of breast ducts and glands. This type is more common among women with BRCA1 gene mutations. For reasons that are not well understood, this cancer is also more common among younger and African-American women.
Spread of breast carcinomas

- Directly into skin and muscle
- Via lymphatics to axillary and other local lymph nodes
- Via bloodstream to lungs, bone, liver and brain
- May be considerable delay before metastasis occurs

Via lymphatics. The axillary lymph nodes are the commonest initial site of metastasis via lymphatics, and between 40 and 50% of women with breast carcinoma will have axillary lymph node metastases at the time of presentation. It is important that the lymph nodes are examined histologically, since clinical palpation is not always reliable. Metastasis to intramammary, supraclavicular and tracheobronchial lymph nodes also occurs.
Paget’s disease of the nipple

- Erosion of the nipple resembling eczema
- Associated with underlying intraduct or infiltrating carcinoma

Clinically, there is roughening, reddening and slight ulceration of the nipple, similar to the skin changes of eczema. Recognition is important, since it is associated with an underlying carcinoma, mainly in the subareolar region. Paget’s disease of the nipple occurs with about 2% of all breast carcinomas, and is associated with a higher frequency of multicentric breast carcinomas.

Within the epidermis of the nipple, large, pale-staining malignant cells can be seen histologically and these cause the changes seen clinically. The malignant cells have now been shown to be derived from the adjacent breast carcinomas. A direct connection may not be seen.
Li-Fraumeni: autosomal dominant; soft tissue and bone sarcomas; breast cancers, brain tumors

Cowden’s disease: autosomal dominant; germline mutation of PTEN; breast and endometrium carcinomas

Ataxia telangiectasia: autosomal recessive; two- to threefold risk for breast cancer
BRCA1 (17q21) and BRCA2 (13q12) syndromes

- Autosomal dominant
- Incidence: 0.12% - 0.14%
- Risk of breast cancer by age 70 years: 65% (BRCA1), 45% (BRCA2)
- Other tumors: ovary, colon, liver (BRCA1), ovary, prostate, pancreas (BRCA2)
- Young age, > 80% basal-like phenotype (BRCA1), luminal phenotype (BRCA2)
**TNM**

T1  Tumour 20 mm or less; no fixation or nipple retraction. Includes Paget’s disease

T2  Tumour 20-50 mm, or less than 20 mm but with tethering

T3  Tumour greater than 50 mm but less than 100 mm; or less than 50 mm but with infiltration, ulceration or fixation

T4  Any tumour with ulceration or infiltration wide of it, or chest wall fixation, or greater than 100 mm in diameter

N0  Node-negative

N1  Axillary nodes mobile

N2  Axillary nodes fixed

N3  Supraventricular nodes or oedema of arm

M0  No distant metastases

M1  Distant metastases
Breast carcinomas in men

About 1% of breast carcinomas occur in males, but the incidence varies throughout the world. It is rare in young men. There is an increased risk in patients with Klinefelter’s syndrome, but no other risk factors have been identified.
Phyllodes tumours can occur at any age, but the median age is 45 years. This is older than for fibroadenoma and the incidence of phyllodes tumours is considerably lower. Phyllodes tumours present clinically as a discrete lump. Macroscopically, they are circumscribed and vary in size up to as much as 450 mm in diameter. They may have both soft and firm areas.

Recurrence is a major problem with phyllodes tumours. The risk of recurrence is less if the tumours are small, with a low mitotic rate and minimal cellular atypia, and have a rounded rather than an infiltrative edge.

In one series of cases, recurrence occurred in 30% of cases and 16% died of metastatic disease.
Phyllodes tumors have two characteristic parts, epithelium and stroma. The epithelium covers large, club-like projections which push into cystic spaces. The stroma is much more cellular than that of fibroadenomas, and can vary in type within the same tumor. The cells may resemble fibroblasts, or they may show marked pleomorphism with mitotic figures. In some tumors, the stromal changes are so marked that they have the appearances of sarcomas.
Gestational trophoblastic disease-general
Related to trophoblastic proliferation
Includes tumors (hydatidiform mole, choriocarcinoma,)
Tumors are uncommon (1/1000 pregnancies)
Patients at extremes of reproductive age are at higher risk to develop complete mole;
no age effect for partial moles; paternal age apparently irrelevant
**Treatment for tumors:** methotrexate; effective even if tumor widely metastatic
(cure rates close to 100%), follow with serum hCG (human Chorionic Gonadotropin)

**NIH classification**
Benign (complete, partial mole)
Malignant, nonmetastatic
Malignant, metastatic
Good prognosis, low risk
Poor prognosis, high risk: duration > 4 months, pretreatment hCG > 40,000, brain or
liver metastases, failed therapy

**Hydatidiform moles-general**
Abnormal placenta with marked enlargement of chorionic villi caused by central edema
of stroma, abnormal blood vessels, **high serum hCG that increases more rapidly than
normal**, variable trophoblastic hyperplasia either complete or incomplete/partial
**Treatment:** curettage, hysterectomy
Complete mole
Caused by abnormal gametogenesis and fertilization; all nuclear DNA is paternal, none is maternal, usually is no fetus

Gross: placenta has grape-like appearance, villi fill uterus, exhibit hydropic degeneration, no embryo present
**Micro:** trophoblastic proliferation AND edema of villi, central cistern formation
villi usually avascular, may exhibit atypia, **Molecular:** 50% diploid, 43% tetraploid,
ploidy analysis useful for diagnosis
Diploid moles - 85% are 46 XX and both X are androgenic ("daddy's girl", empty ovum
is fertilized by sperm that duplicates without cytokinesis, no maternal nuclear DNA,
but there is maternal mitochondrial DNA)
Incomplete / partial mole
20% of all moles; triploid
Contain extra set of paternal chromosomes, either from second sperm or one diploid sperm (diandric)
Embryo is usually present, although often abnormal
Micro: mixture of edematous villi similar to complete mole and relatively normal villi mild trophoblast hyperplasia without atypia
Molecular: 58% XXY; 40% XXX; 2% XYY; ploidy analysis useful for diagnosis
Choriocarcinoma
Most aggressive form of gestational trophoblastic disease
Carcinoma derived from trophoblastic cells secondary to a prior pregnancy (normal or abnormal)
**Incidence:** 1 per 40 moles (usually complete), 1 per 150,000 normal pregnancies
**Clinical:** usually arises from uterus or elsewhere if ectopic pregnancy; bloody, brown, foul-smelling discharge
Rapidly invasive and metastasizing; may present with metastases but have small or necrotic primary tumor
**Metastases commonly to lungs;** Serum hCG ~ 18,000,
**Gross:** soft, fleshy, yellow-white, necrotic, hemorrhagic; may be microscopic or large
**Micro:** mixture of cytotrophoblast and syncytiotrophoblast in plexiform pattern; may have marked nuclear pleomorphism and hyperchromasia; extensive necrosis with minimal trophoblastic tissue; prominent vascular invasion