V. FEMALE GENITAL SYSTEM PATHOLOGY

UTERINE CERVIX DISORDERS

CERVICITIS. The inflammation of the cervix (endo+exocervix) is related to its constant exposure to the bacterial flora in the vagina. Acute and chronic cervicitis results from infection with many microorganisms such as Streptococcus, Staphylococcus, Neisseria gonorrhoeae, Chlamydia, Herpes simplex virus. Some agents are sexually transmitted, whereas others may be introduced during childbirth with lacerations of cervix or by foreign bodies.

A special part is reserved to Human papillomavirus infection because, depending on the subtype, the cervical lesions range from genital warts (condyloma acuminata – HPV 6 and 11 = low-risk HPV types) to high-grade CIN or invasive cancers (see further) – HPV 16 and 18 = high-risk HPV types, respectively HPV types 31, 33 and 35 = intermediate-risk HPV types.

Condylomata acuminata are benign genital warts caused by low oncogenic risk HPVs, mainly types 6 and 11. They may be solitary, but are more frequently multifocal. On histologic examination, they consist of papillary, exophytic, treelike cores of stroma covered by thickened squamous epithelium. The surface epithelium shows characteristic viral cytopathic changes referred to as *koilocytic atypia*, which manifest as nuclear enlargement, hyperchromasia and a cytoplasmic perinuclear halo. Condylomata acuminata are not precancerous lesions.

In **acute cervicitis,** the cervix is grossly red, swollen and edematous, with copious pus "dripping" from the external os (bacterial endocervicitis). Microscopically, the tissues exhibit an extensive infiltrate of polymorphonuclear leukocytes and stromal edema.

In **chronic cervicitis,** which is more common, on colposcopic examination cervical mucosa is hyperemic and there may be true epithelial erosions. Microscopically, there is a loss of the epithelial (stratified squamous type) lining = erosion / ulceration and a massive inflammatory infiltrate (a mixture of polymorphs, lymphocytes, plasma cells and histiocytes). The superficial part of the erosion presents necrotic material and beneath, the inflammatory cells accumulation and the proliferation of the granulation tissue. Numerous hyperemic new-formed capillaries with endothelial cells swelling, inflammatory cell perivascular cuffs and prominent interstitial edema are found. The inflammatory infiltrate is diffusely spread or, sometimes, can aggregate to form lymphoid follicles.

BENIGN TUMORS.

1. *endocervical polyp* a single, smooth, or lobulated mass. It's superficial lining epithelium is mucinous, with varying degrees of squamous metaplasia.
2. *microglandular hyperplasia* is characterized by closely packed endocervical glands that lack an intervening stroma, cause by progestin overstimulation (during pregnancy, postpartum period, oral contraceptives).
3. *leiomyoma* of the cervix similar to that of it's uterine body counterpart, becomes symptomatic by bleeding or by prolapsing into the endocervical canal, an event that leads to uterine contractions and pain resembling the early phases of labor.

MALIGNANT TUMORS.

1. Intraepithelial and invasive squamous neoplasia

Today is documented that the whole spectrum of epithelial changes (from mild dysplasia through more marked intraepithelial abnormalities to invasive squamous cell carcinoma) begins at the squamocolumnar junction. This junction doesn't have a fixed position during life, it is movable upward and downward through cervical os, depending on hormonal stimulation – endogenous and exogenous -, and childbirth. In most young women the columnar epithelium extends onto the exocervix, outside the os, into vagina. The vaginal environment (acidic pH, bacteria, trauma) stimulates the conversion of mucinous columnar cells to squamous metaplastic cells, better adapted to this kind of environment. The process ends when the entire single layer columnar epithelium situated outside the os is replaced by a stratified squamous epithelium. The squamous metaplasia is restricted to the superficial lining of the mucosa, in the depth of glandular pouches the mucinous epithelium is preserved, hence the situation of endocervical glands beneath a squamous epithelium that can block

their outlet, leading to cystic dilatations of these glands, termed *nabothian cysts.* ***The area between the original squamocolumnar junction on the exocervix and the new squamocolumnar junction at the internal os is termed the*** transformation zone. In the course of these events: squamous metaplasia, progressive maturation of this metaplastic epithelium, the transformation zone may display intraepithelial abnormalities or varying degree of dysplasia, termed cervical intraepithelial neoplasia (CIN). Dysplasia in the cervical epithelium implies an alteration that carries with it the potential for malignant transformation:

CIN-1: mild dysplasia – cells of basal third of epithelium show atypia: pleomorphic nuclei, high nucleo/cytoplasmatic ratio, mitoses, loss of cellular polarity. The upper two thirds of epithelium are normally matured and stratified.

CIN-2: moderate dysplasia - cells of basal two thirds of epithelium show atypia, the upper third is normal.

CIN-3: severe dysplasia / carcinoma *in situ* – the malignant lesion involves the entire thickness of the squamous epithelium, but it is confined to the basement membrane, so the underlying stroma isn't invaded.

An alternative grading system divides these lesions into low- and high-grade squamous intraepithelial lesions (SILs), with low-grade SIL corresponding approximately to CIN 1 and high-grade SIL to CIN 2 and 3.

More than 80% of LSILs and 100% of HSILs are associated with high-risk HPVs, with HPV-16 being the most common HPV type in both categories of lesions.

The normal process by which cervical squamous epithelium matures is disturbed across the full thickness of SIL, as evidenced by changes in cellularity, differentiation, polarity, nuclear features and mitotic activity. The height to which the basaloid cells extend upward in the epithelium differs from CIN system. The most dramatic changes in **LSIL (CIN-1)** occur not in the base, but rather in koilocytes of the superficial epithelium, which show ballooned cytoplasm and irregular large nuclei caused by episomal virus propagation within differentiated squamous cells that are absent in the base. Features in the basal region related to genomic integration of virus in propagating basal cells are prominent in **HSIL (CIN-2/-3)**. These include disorganization of basal cell alignment along the basement membrane and nuclear changes that persist as cells are pushed upward in the epithelium.

All this spectrum of intraepithelial changes can be detected by the Papanicolaou smear long before invasion has occurred, explaining why the incidence of cervical cancer has been halved and the mortality rate has fallen in the last 50 years.

70% of cases of LSIL regress, 6% progress to HSIL and less than 1% become invasive cancer. Progression of HSIL to invasive squamous carcinoma occurs with greater frequency and over a shorter interval, but the exact figures vary with intervening management. 10% to 20% of cases of HSIL progress to invasive carcinoma if untreated.

Biopsy is indicated when SIL is discovered on Pap smear. Targeted biopsies may be visually directed by colposcopy, or the entire transformation zone can be removed by a wire "loop" electrosurgical excision procedure (LEEP). High-grade lesions are treated by ablation methods determined by their anatomic distribution. LEEP may be sufficient, if margins are negative. Cervical conization (removal of a cone of tissue around the external os), cryosurgery and (rarely) hysterectomy may also be done. Follow-up smears and clinical examinations should continue for life.

Superficially invasive squamous cell carcinoma (formerly known as microinvasive squamous cell carcinoma) is the earliest stage of invasive cervical cancer and it is characterized by minimal invasion (based on depth and width) of the stroma by neoplastic cells, in the absence of vascular invasion and lymph node metastases. Because tumors at this stage are not grossly visible, the microscopic criteria used for their diagnosis are:

- the depth of invasion less than 3 mm from the basement membrane point of origin
- the width of invasion less than or equal to 7 mm maximum lateral extension

The recognizable (by microscope examnination) invasive changes are tiny irregular epithelial buds emanating from the base of HSILs. These small tongues of neoplastic epithelial cells, beneath the basement menbrane do not affect the prognosis of HSILs; hence, both can be treated similarly with conservative surgery.

Invasive squamous cell carcinoma is by far the most common type of cervical cancer. The term "invasive" means that the carcinomatous cells are found over 3 mm below the basement membrane, so the spreading by direct extension (ureterus, urinary bladder, rectum) or through lymphatics (regional lymph nodes involvement) can be present.

Cervical cancer presents itself as a poorly defined, granular and eroded lesion (ulcerating pattern), as an exophytic mass (fungating pattern), as an endophytic mass (infiltrative pattern, causing enlargement and hardening of the cervix – "barrel shaped" cervix) or as a combination of these patterns of growing.

On microscopic examination, the majority of tumors display a large cell *nonkeratinizing* pattern, (moderately differentiated) – with solid nests of large malignant squamous cells without keratinization. Most of the remaining cancers are *keratinizing* (well-differentiated), exhibiting nests of keratinized cells arranged in concentric whorls, so-called "keratin pearls". The least common pattern of cervical cancer is *small cell carcinoma.* This tumor consists of infiltrating masses of small, cohesive, malignant cells that are not keratinized, being with neuroendocrine differentiation (positive markers: chromogranin, synaptophysin).

2. Adenocarcinoma

The incidence of cervical adenocarcinoma has increased recently (from 10% of malignant cervical tumors considered in the past), with a mean age of 56 years at presentation. Most tumors originated in endocervical glands so they are endocervical cell (mucinous) type and similar to exocervical cancer, they have an *in situ* form or an *invasive* one. Invasive adenocarcinoma with pseudoglands and solid masses invading the stroma is often associated with adenocarcinoma in situ and contains HPV types 16 or 18.

Adenocarcinoma in situ also called **cervical glandular intraepithelial neoplasia,** generally arises at the squamocolumnar junction and extends into the endocervical canal. It displays tall columnar cells with eosinophilic or mucinous cytoplasm, sometimes resembling goblet cells. The pattern of spread and involvement of endocervical glands resemble those of exocervical SIL. Adenocarcinoma in situ typically is intraepithelial, maintaining normal endocervical gland architecture, but the cells show slight enlargement, atypical hyperchromatic nuclei, increased nuclear-to-cytoplasmic ratio and variable mitoses.

Invasive adenocarcinoma typically presents as a fungating polypoid or papillary mass. Exophytic tumors often have (microscopically) a papillary pattern, whereas endophytic ones display tubular or glandular patterns. Poorly differentiated tumors are predominantly composed of solid sheets of cells. Adenocarcinoma of the endocervix spreads by local invasion and lymphatic metastases, but overall survival is somewhat worse than for the invasive squamous carcinoma.

The prognosis and survival for cervical invasive carcinomas depend on the stage of the cancer at diagnosis and to some degree on histologic subtype, with small-cell neuroendocrine tumors having a very poor prognosis.

Stage I Confined to the cervix
- A. Microscopic invasion (≤ 3 mm deep and ≤ 7 mm wide)
- B. Clinically visible or dimensions greater than IA

Stage II Tumour invades beyond the uterus but not to the pelvic wall or lower third of the vagina

Stage III Tumour extends to the pelvic wall and/or involves the lower third of the vagina and/or causes hydronephrosis or non-functioning kidney

Stage IV Involves (biopsy proven) the mucosa of the bladder or rectum and/or extends beyond the true pelvis (including metastasis).

With current treatments the 5-year survival rate is 100% for superficially invasive (microinvasive) carcinomas and less than 50% for tumors extending beyond pelvis. The more advanced stages at the time of diagnosis are not surgically resectable and are managed with combined chemotherapy and radiotherapy (chemo-radiation).

UTERINE BODY DISORDERS

ENDOMETRITIS. The inflammation of the endometrium is a histologic diagnosis based on the finding of an abnormal inflammatory cell infiltrate in the endometrium. It must be distinguished from the normal presence of polymorphonuclear leukocytes during menstruation and a mild lymphocytic infiltrate at other times.

Acute endometritis is always associated with parturition and septic abortion. Most cases result from an ascending infection from the cervix (e.g. after the cervical barrier is compromised by abortion, delivery or medical instrumentation). Infection at the time of parturition is commonly associated with retention of products of conception.

A mixed bacterial flora, formed by pyococci, coliform organisms and proteus is present. The usual acute inflammatory changes take place (vascular hyperemia, massive polymorph infiltration, edema). Curettage is diagnostic and often curative, because it removes the necrotic tissue that has served as the nidus of ongoing infection.

The following complication can occur: (1) puerperal sepsis, (2) myometritis, (3) parametritis with iliac venous thrombosis, (4) salpingitis with subsequent tubal blockage and infertility, (5) peritonitis through fallopian tube; but all of these conditions are seldom nowadays - the antibiotic era.

Chronic endometritis is associated with IUD (intrauterine devices) use, pelvic inflammatory disease, and retained products of conception after an abortion or delivery. The histopathological diagnosis of chronic endometritis is based on the presence of plasma cells in the endometrium. The condition is generally self-limited. A particular case is that of **tuberculous endometritis,** when bacillary infestation spreads from the fallopian tubes or, less common, from bloodstream, in generalized miliary. If the woman is still menstruating, the tubercles are shed each month. In some cases, menstruation ceases and caseation occurs.

ADENOMYOSIS is the presence of endometrial glands and stroma within the myometrium. Pain, dysmenorrhea or menorrhagia correlate with adenomyosis if the glands are 1 mm or more beneath the endometrial myometrial junction, with more severe symptoms as glands penetrate more deeply into the myometrium. Pain occurs as foci of adenomyosis enlarge when blood is entrapped during menses. One fifth of all uteri surgically removed show some adenomyosis.

Grossly, the uterus may be enlarged. The myometrium discloses small, soft, tan areas, some of which are cystic. Microscopic examination shows glands lined by proliferative to inactive endometrium and surrounded by endometrial stroma with varying degrees of fibrosis.

ENDOMETRIOSIS is defined as the presence of benign endometrial glands and stroma outside the uterus. The sites most frequently involved are the ovaries, the uterine ligaments, the pouch of Douglas, and the pelvic peritoneum. Sometimes, endometriosis can be more widespread involving cervix, vagina, perineum, bladder, umbilicus, and pelvic lymph nodes. On rare occasions distant areas such as lungs, pleura, small bowel, kidneys, and bones may be affected.

The pathogenesis of endometriosis considers several theories such as: *menstrual implantation* – foci of menstrual endometrium regurgitate through the fallopian tubes and implant on the various pelvic organs; *intraoperative implantation* – following hysterotomy and episiotomy; *lymphatic and hematogenous dissemination.*

In the most common sites – ovary and the peritoneal surface – endometriosis appears as red or bluish nodules, which vary from 1 to 5 mm. Since the ectopic endometrial glands often participate in the menstrual cycle, repeated bleeding leads to the deposition of hemosiderin and a grossly brown discoloration. Microscopically, endometriosis is diagnosed by the presence of ectopic endometrial glands and stroma. On occasion healed foci of endometriosis consist only of fibrous tissue and hemosiderin-laden macrophages.

ENDOMETRIAL HYPERPLASIA and ENDOMETRIAL CARCINOMA represent a broad spectrum of proliferative disease that constitutes a morphologic and biologic continuum, similar to multistep carcinogenesis in other tissues. Thus, the lesions progress from the mildest degrees of

hyperplasia of endometrial glands to invasive cancer. Proliferative lesions of the endometrium often reflect hyperestrinism / *prolonged estrogenic stimulation of the endometrium*.

Endometrial hyperplasia is an important cause of abnormal uterine bleeding and a frequent precursor to the most common type of endometrial carcinoma. It is defined as an increased proliferation of the endometrial glands relative to the stroma, resulting in an increased gland-to-stroma ratio when compared with normal proliferative endometrium. Endometrial hyperplasia is associated with prolonged high levels of estrogen, which can be due to anovulation, increased estrogen production from endogenous sources, or exogenous estrogen. Associated conditions include:

• Obesity (peripheral conversion of androgens to estrogens)
• Menopause and estrogen replacement therapy: to control its symptoms
• Polycystic ovarian syndrome
• Functioning granulosa cell tumors of the ovary
• Excessive ovarian cortical function (cortical stromal hyperplasia)
• Prolonged administration of estrogenic substances.

The classification of endometrial hyperplasia has undergone a number of changes over the years to keep pace with new insights into the disorder. In the recent past, the most widely used system divided endometrial hyperplasia into four categories: simple hyperplasia without atypia; complex hyperplasia without atypia; simple atypical hyperplasia; and complex atypical hyperplsia. However, the most current World Health Organization (WHO) classification recommends collapsing the four categories into two major categories: non-atypical hyperplasia and atypical hyperplasia (also referred to as *endometrial intraepithelial neoplasia / EIN*),which differ in appearance and in their propensity to progress to carcinoma. Women newly diagnosed with EIN have a 30% to 40% chance of having endometrial cancer diagnosed within 1 year.

- **Non-atypical hyperplasia** has a wide-range of appearances, but the cardinal feature is an increase in the gland-to-stroma ratio. The glands show variation in size and shape and may be dilated. Although there may be back-to-back glands focally, some intervening stroma is usually retained. Some of the glands are straight, small tubular structures lined by a tall, tightly packed, basophilic cells, with no cytological atypia. These lesions reflect an endometrial response to persistent estrogen stimulation and rarely progress to adenocarcinoma (approximately 1% to 3%). Non-atypical hyperplasia may evolve into cystic atrophy when estrogen is withdrawn.
- **Atypical hyperplasia (endometrial intraepithelial neoplasia)** is composed of complex patterns of proliferating glands displaying nuclear atypia. The glands are commonly back-to-back and often have complex outlines due to branching structures. Individual cells are rounded and lose the normal perpendicular orientation to the basement membrane. In addition, the nuclei have open (vesicular) chromatin and conspicuous nucleoli. The features of atypical hyperplasia have considerable overlap with those of well-differentiated endometrioid adenocarcinoma, and accurate distinction from cancer may not be possible without hysterectomy. Approximately 23% to 48% of women with a diagnosis of atypical hyperplasia are found to have carcinoma when a hysterectomy is performed.

Of note:

- ✓ Endometrial hyperplasia is defined as an increase in the number of glands relative to the stroma, appreciated as crowded glands, often with abnormal shapes.
- ✓ It is most commonly caused by unopposed estrogen stimulation and is an important cause of abnormal vaginal bleeding.
- ✓ It is divided into non-atypical and atypical hyperplasia based on nuclear atypia. Atypical hyperplasia is associated with an increased risk of endometrial carcinoma.
- ✓ Currently, atypical hyperplasia is managed by hysterectomy or, in young women who desire fertility, a trial of progestin therapy and close follow-up.

Endometrial carcinoma arises, commonly, in peri- or postmenopausal women, typically > 50 and is uncommon in those aged < 40. Most endometrial carcinomas present a non-specific abnormal vaginal bleeding.

Endometrial carcinoma (most common an adenocarcinoma, characterized by more or less well-defined glandular pattern) is broadly grouped into two histologic types. Type I tumors (about 80% - 85%), *endometrioid* carcinomas, often arise from EIN precursors and are associated with estrogenic stimulation. They occur mainly in pre- or perimenopausal women and are associated with obesity, hyperlipidemia, anovulation, infertility and late menopause. Most endometrioid carcinomas are confined to the uterus and follow a favorable course.

In contrast, type II tumors are *nonendometrioid*, largely papillary serous carcinomas. Type II tumors are not associated with estrogen stimulation or endometrial hyperplasia, readily invade myometrium and vascular spaces and are highly lethal.

Grossly, these types have common features, growing in a diffuse or a localized polypoid pattern, presenting areas of necrosis and hemorrhage. Spread occurs by direct continuity with the invasion of myometrium and periuterine structures

Histologically, *endometrioid carcinoma* (the most common histologic variant) is composed entirely of glandular cells, divided into three grades depending on the ratio of glandular to solid elements, the latter signifying poorer differentiation:

Grade 1: Well differentiated; almost only neoplastic glands, with minimal (<5%) solid areas
Grade 2: Moderately differentiated; 5% – 50% of malignant cells form solid areas
Grade 3: Poorly differentiated; large (> 50%) areas of solid tumor.

Nuclei of endometrial adenocarcinoma range from bland to markedly pleomorphic, usually with prominent nucleoli. Mitoses are abundant and abnormal in less differentiated tumors.

Nonendometrioid types of endometrial carcinoma are less common. These generally occur in women who are about 10 years older than those with type I carcinomas, and in contrast to type I carcinoma they usually arise in the setting of *endometrial atrophy*. Type II tumors are by definition poorly differentiated (grade 3) tumors and account for approximately 15% of cases of endometrial carcinoma. The most common subtype is *serous carcinoma*, referred to as such because of morphologic and biologic overlap with ovarian serous carcinoma (discussed later in this chapter). Several less common histologic subtypes (clear cell carcinoma and malignant mixed müllerian tumor) are also included within this category.

The therapy and prognosis depend on the clinical stage of the disease when discovered and its histologic grade and type. Women with well-differentiated tumors confined to the endometrium are treated by hysterectomy. Postoperative radiation is administrated if the tumor is poorly differentiated, the myometrium is more than superficially invaded, or the cervix is involved.

Pathologic staging of both type I and II endometrial adenocarcinoma is as follows:

Stage I - Carcinoma is confined to the corpus uteri itself.
Stage II - Carcinoma involves the corpus and the cervix.
Stage III - Carcinoma extends outside the uterus but not outside the true pelvis.
Stage IV - Carcinoma extends outside the true pelvis or involves the mucosa of the bladder or the rectum.

LEIOMYOMA. It is the benign tumor of smooth muscle origin and the most common tumor of female genital tract. Grossly, leiomyomas of the uterus are hard, round, white or pale gray, encapsulated and with a whorled appearance on the cut surface. They range in size from 1 mm to more than 30 cm in diameter. Most leiomyomas are intramural, but some are submucosal, subserosal with (forming a pedunculated polyp) or without pedicle.

Microscopically, leiomyomas are composed of interlacing fascicle of uniform spindle cells, in which the nuclei are elongated and have blunt ends. The cytoplasm is abundant, eosinophilic and fibrillar.

Complications:

- hyaline or mucoid degeneration ± calcification
- necrosis and hemorrhage (submucous leiomyoma)

- torsion (subserous leiomyoma)
- malignant transformation = **leiomyosarcoma** when there is nuclear atypia and more than 4 mitoses / 10 high-power microscopic fields.

FALLOPIAN TUBES DISORDERS

Acute and **chronic** SALPINGITIS typically results from ascending infections of the lower genital tract. The most common causative organisms are N. gonorrhoeae, E. coli, Chlamydia and Mycoplasma. Typically, the infection is polymicrobial. The acute episodes, particularly those associated with chlamydial infection, may be asymptomatic. In most cases, chronic salpingitis develops only after repeated episodes of acute salpingitis. Uncommonly, salpingitis is a primary infection within the fallopian tube or represents a secondary spread of infection from a nearly perforated viscus, such as the appendix.

In **acute salpingitis** microscopic examination reveals a marked inflammatory infiltrate of polymorphonuclear leukocytes, in association with marked edema and congestion of the mucosal folds.

The fallopian tubes allow ascending microorganisms from the lower genital tract to reach the peritoneal cavity, a journey that leads to peritonitis and pelvic inflammatory disease. The adjacent ovary may also be involved in the process, sometimes giving rise to a **tubo-ovarian abscess**.

The inflammatory infiltrate in **chronic salpingitis** is composed of lymphocytes and plasma cells; the edema and congestion tend to be minimal. In late stages, the fallopian tube may seal and become distended with pus (**pyosalpinx**) or an acellular transudate (**hydrosalpinx**).

The damage wrought by chronic salpingitis often poses a mechanical obstruction to the passage of sperm, in which case infertility results. Also, chronic salpingitis is a common cause of ectopic pregnancy, since adherent mucosal plicae create pockets in which ova can become entrapped.

ECTOPIC PREGNANCY refers to any implantation that develops outside the endometrium. Over 95% of ectopic pregnancies occur in the fallopian tube, mostly in the distal and middle thirds. An ectopic pregnancy results when the passage of the conceptus along the fallopian tube is impeded, for example, by mucosal adhesion or abnormal tubal motility secondary to inflammatory disease or endometriosis. The trophoblast readily penetrates the mucosa and wall of the tube. The thin tubal wall usually ruptures by the l2th week of gestation. Tubal rupture is life threatening, because it can result in rapidly exanguinating hemorrhage.

OVARIAN PATHOLOGY

NON-NEOPLASTIC CYSTS are the most common cause of enlarged ovaries. Excluding cysts that arise from the invaginated surface epithelium of the ovary (serous cysts) almost all arise from ovarian follicles.

Follicle cyst is thin-walled, fluid-filled structure that is lined internally by granulosa cells and externally by a layer of theca interna cells. Rarely exceed 5 cm in diameter and occur at any age up to the menopause. Follicular cysts are unilocular and may be single or multiple, unilateral or bilateral. It arises from ovarian follicles and are probably related to abnormalities in the release of pituitary gonadotropins. If the cyst persists, the hormonal output can lead to precocious puberty in a child and menstrual irregularities in the adult. The only significant complication is mild intraperitoneal bleeding.

Corpus luteum cyst results from the delayed resolution of the central cavity of a corpus luteum. Continued progesterone synthesis leads to menstrual irregularities. A corpus luteum cyst is typically unilocular and 3 to 5 cm in diameter, with a yellow wall. The contents of the cyst vary from serosanguineous fluid to clotted blood. Microscopic examination shows numerous, large luteinized granulosa cells.

Polycystic ovary syndrome (Stein-Leventhal syndrome) was described initially as secondary amenorrhea, hirsutism, and obesity.

On gross examination both ovaries are enlarged. The surface is smooth, an appearance reflecting the absence of ovulation. On cut section, the cortex is thickening and numerous subcortical cysts, typically less than 1 cm in diameter, are seen. Microscopically, the following features are

present: numerous follicles in early stages of development, follicular atresia, stroma with luteinized cells (hyperthecosis), and morphologic signs of an absence of ovulation (thick, smooth capsule and absence of corpora lutea and corpora albicantia). Many of the subcapsular cysts are lined by thick zones of theca interna, some cells of this structure may be luteinized.

TUMORS. There are more than 25 major types of ovarian neoplasms. With variants and rare entities, they number nearly 100. The most frequently encountered tumors arise from the surface epithelium and are termed common epithelial tumors. Other important groups include germ cell tumors, sex cord/stromal tumors, and metastatic tumors to the ovary.

1. Common epithelial tumors.

Benign common epithelial tumors are almost always serous or mucinous and generally arise in women between the age of 20 and 60 years. They are frequently large, 15 - 30 cm in diamater. Some of these tumors, partricularly the mucinous variety, reach truly massive proportion, exceeding 50 cm in diameter. Benign epithelial tumors are typically cystic, hence the term *cystadenoma*. *Serous cystadenomas* are more commonly bilateral (15%) than *mucinous cystadenomas* and tend to be unilocular. By contrast, mucinous tumors are characteristically composed of hundreds of small cysts. As opposed to their malignant counterparts, benign epithelial tumors of the ovary tend to have thin walls and lack solid areas. Microscopically, a single layer of tall columnar epithelium lines the cysts. Papillae, when present, consist of fibrovascular core covered by a single layer of tall columnar epithelium identical to that of the cyst lining.

Up to 5% of mucinous tumors of the ovary are complicated by the implantation of numerous mucus-producing cells on the peritoneal surfaces. This results in the massive accumulation of gelatinous material in the abdominal cavity, similar to that seen in *pseudomyxoma peritonei* associated with mucocele of the appendix. Some believes that these lesions represent metastases from mucinous tumors of low malignant potential. Histologically, the peritoneal implants are composed of regular, mucus-containing columnar cells, without atypia and mitoses.

Brenner tumor. The typical Brenner tumor is benign and occurs at all ages, with half of the cases presenting in women over 50 years of age. The size varies from a microscopic focus to masses as large as 8 cm or more in diameter. Histologically, Brenner tumor is composed of solid nests of transitional-like (urothelium-like) cells enclosed in a dense, fibrous stroma. The most superficial epithelial cells may exhibit mucinous differentiation. A small number of cases are of low malignant potential (proliferative Brenner tumor). Frankly malignant tumors are exceedingly rare.

Borderline tumors (tumors of low malignant potential). The designation “borderline malignancy” is an important concept of recent vintage. It refers to a group of ovarian tumors that share an excellent prognosis, despite certain histologic features that suggest cancer. These are characterized by epithelial cell proliferation and nuclear atypia, but not destructive stromal invasion. Despite histologic features suggesting aggressiveness, they share an excellent prognosis.

A surgical cure is almost always possible if the tumor is confined to the ovaries. Even when it has spread to the pelvis or abdomen, 80% of patients are alive after 5 years. Borderline tumors generally occur in women between the ages of 20 and 60 years.

Serous tumors of borderline malignancy are more commonly bilateral (34%) than mucinous ones (6%) or other types. The tumors are of variable size. Mucinous tumors sometimes achieve gigantic size and weight (25 kg). In serous tumors of borderline malignancy, it is common to find papillary projections, ranging from fine to clusters of grape-like structures, arising from one or several sites of the cyst wall. Microscopically, these structures resemble the papillary fronds in benign cystadenoma but are distinguished from them by epithelial stratification, nuclear atypism, and mitotic activity. The same criteria apply to borderline mucinous tumors, although papillary projections are less conspicuous.

By definition, the presence of stromal invasion in the primary tumor removes it from the category of borderline malignancy and identifies it as frankly malignant.

Malignant epithelial tumors of the ovary are most common between the ages of 40 and 60 years and are rare under the age of 35. By the time a carcinoma reaches a size of 10 to l5 cm, it often has already spread beyond the ovary and seeded the peritoneum.

Serous cystadenocarcinoma is the most common malignant ovarian tumor, accounting for a third of all cancers of the ovary. In half the patients, the tumors are bilateral. Since tumors of advanced stage are bilateral more than twice as often as tumors of low stage, it is thought that in many cases the cancer spreads to the other ovary by implantation. On gross examination, serous cystadenocarcinoma usually is a multiloculated tumor, with soft, delicate papillae lining the entire surface. Solid areas, often with zones of necrosis and hemorrhage, are commonly present.

Microscopically, serous cystadenocarcinomas vary from well differentiated to poorly differentiated tumors. In the latter, the papillary pattern may be inconspicuous, with most areas being composed of solid sheets of malignant cells. Stromal and capsular invasion by the tumor cells is evident. Laminated calcified concretions, referred to as psammoma bodies, are present in one third of the cases.

Mucinous cystadenocarcinoma constitute up to 10% of all ovarian cancers. They are among the largest tumors recorded and, as previously noted for their benign counterpart, may attain a size of 50 cm in diameter. In a fourth of the cases, bilateral tumors are present. Mucinous cancers are typically cystic and multilocular, with many solid areas and papillary projections. Microscopically, similar to serous cancers, the appearance ranges from well differentiated to poorly differentieted. The well-differentiated tumors are characterized by neoplastic glands lined by tall columnar, mucin-producing malignant cells. Poorly differentiated mucinous adenocarcinomas show irregular nests and cords of tumor cells and numerous mitoses. Stromal invasion is the rule, and infiltration of the capsule is common.

Endometrioid adenocarcinoma is a tumor of the ovary that histologically is identical to carcinoma of the endometrium. It is second only to serous cystadenocarcinoma in frequency, accounting for 20% of all ovarian cancers. The tumor occurs most commonly after the menopause. One third to one half of endometrioid carcinomas are bilateral.

On gross examination, endometrioid cacinomas vary in size from 2 cm to more than 30 cm in diameter. They tend to be cystic, although some are completely solid and exhibit necrotic areas. Microscopiocally, the tumors are graded according to the same scheme used for endometrial adenocarcinoma. Interestingly, a concomitant endometrial cancer is frequently encountered, the rate in various series ranging from l5% to 50%. The prognosis depends on the stage at which the tumor presents, but the overall survival in endometrial carcinoma is considerably better than that in serous cystadenocarcinomas.

Clear cell adenocarcinoma, which is thought to be closely related to endometrioid adenocarcinoma, is often found in association with endometriosis. It constitutes 5% to l0% of all ovarian cancers, usually occurring after the menopause. The size of the tumors ranges from 2 to 30 cm in diamater, and 40% are bilateral. The majority are partially cystic and exhibit necrosis and hemorrhage in the solid areas. Microscopically, clear cell adenocarcinoma is composed of sheets of malignant cells with clear cytoplasm, or tubules lined by cancer cells. The clinical course parallels that of endometrioid carcinoma.

Survival for patients with malignant ovarian tumors is poor in general. Overall, the 5-years survival is only 35%, because in more than half cases the tumors have spread to the abdominal cavity, or elsewhere, by the time they are discovered.

2. Germ cell tumors. Tumors derived from the germ cells of the ovary represent a fourth of all ovarian tumors. In adult women germ cell tumors are virtually all benign (mature cystic teratoma, dermoid cyst), whereas in children and young adults they are largely malignant. In children, germ cell tumors are the most common form of ovarian cancer (60%); they are rare after the menopause.

Dysgerminoma is the ovarian counterpart of testicular seminoma and is composed of primordial germ cells. Although it accounts for less than 2% of all ovarian cancers, dysgerminoma is responsible for 10% of these cancers in women younger than 20 years of age. The tumors are bilateral in about 15% of cases.

On gross examination, dysgerminomas are often large and firm and have a bosselated external surface. The cut surface is often soft and fleshy. Microscopic examination reveals large nests of monotonous tumor cells, which have a clear glycogen-filled cytoplasm and irregularly flattened central nuclei. Fibrous septa containing lymphocytes traverse the tumor.

The 5-years survival rate for patients with stage I tumors approaches 100%. Because the tumor is highly radiosensitive, 5-years survival rates for higher stage tumors exceed 80%.

Teratoma is a tumor of germ cell origin that shows differentiation toward somatic structures.

a) Mature teratoma (dermoid cyst) is a benign neoplasm, which accounts for one fourth of all ovarian tumors. The peak incidence occurs in the third decade.

Mature teratomas develop by **parthenogenesis**. Haploid (postmeiotic) germ cells endoreduplicate to give rise to diploid genetically female tumor cells (46,XX).

The tumor is cystic, and more than 90% contain skin, sebaceous glands, and hair follicles. Half of the tumors exhibit smooth muscle, sweat gland, cartilage, bone, teeth, and respiratory tract epithelium. Tissues such as gut, thyroid, and brain are encountered less frequently. *Struma ovarii* refers to a cystic lesion composed predominantly of thyroid tissue (5% to 20% of mature cystic teratomas). A small minority (1%) of dermoid cysts undergo malignant transformation. These cancers usually occur in older women.

b) Immature teratoma of the ovary is composed of elements derived from the three germ layers. It contains immature or embryonal tissues. Immature teratoma is predominantly solid and lobulated and contains numerous small cysts. Microscopically, multiple tumor components are usually found, including those differentiating toward nervous tissue (neuroepithelial rosettes and imature glia), glands, and other structures found in mature cystic teratomas.

Endodermal sinus tumor (Yolk sac carcinoma) is a highly malignant tumor of women younger than 30 years of age that histologically resembles the mesenchyme of the primitive yolk sac. Typically, the endodermal sinus tumor is large and displays extensive necrosis and hemorrhage. Microscopic examination reveals multiple patterns. The most common appearance is a reticular, honeycombed pattern of communicating spaces lined by primitive cells. Schiller-Duval bodies are characteristic of the tumor. These structures consist of papillae that protrude into a space lined by tumor cell. The papillae are covered by a mantle of embryonal cells and contain a fibrovascular core and a central blood vessel.

Gonadoblastoma is a distinctive ovarian tumor because of its association with various types of gonadal dysgenesis. The majority of affected women is virilized and suffers from primary amenorrhea and developmental abnormalities of the genitalia. Microscopically, cellular nests composed of a mixture of germ cells and sex cord derivates, resembling immature Sertoli and granulosa cells, are present.

3. Sex cord/stromal tumors. Tumors of the sex cord and stroma are derived from either the primitive sex cords or the mesenchymal stroma of the developing gonad. They account for 10% of all ovarian tumors. The tumors range from benign to low grade malignant and are frequently differentiated towards female (granulosa and theca cells) or male (Sertoli and Leydig cells) structures. Sex cord/stromal tumors account for most of the clinically functional ovarian tumors.

Ovarian fibroma is the most common ovarian stromal tumor. It occurs at all ages, with a peak in the perimenopausal period, and is virtually always benign. The tumor is solid, firm, and white. Microscopically, the cells resemble the stroma of the normal ovarian cortex, being composed of well-differentiated fibroblasts and variable amounts of collagen. Half of the larger tumors are associated with ascites and, rarely, with ascites and pleural effusions (Meigs syndrome).

Thecoma is a functional ovarian tumor that arises in postmenopausal women. In the majority of cases it produces signs of estrogen production. Thecomas are solid tumors, mostly 5 to 10 cm in diameter. The cut section is yellow, owing to the presence of many lipid-laden theca cells. Microscopically, the cells are large and oval to round, with a vacuolated cytoplasm that contains lipid. Bands of hyalinized collagen separate nests of theca cells. Thecomas are virtually always benign. Because of estrogen output by the tumor, thecomas commonly cause irregularity in menstrual cycles and breast enlargement. Endometrial hyperplasia or cancer may be the complications of the tumor.

Granulosa cell tumor is the prototypical functional neoplasm associated with estrogen secretion. This tumor should be considered malignant, because of its potential for local spread and the rare occurrence of distant metastases. Most granulosa cell tumors occur after the menopause, and they are unusual before puberty.

Granulosa cell tumors are large and focally cystic to solid. Characteristically, the tumor has yellow areas, representing lipid-laden luteinized granulosa cells, white zones of stroma, and focal hemorrhages. Microscopically, granulosa cell tumors display an array of growth patterns: (1) diffuse (sarcomatoid), (2) insular (islands of cells), or (3) trabecular (anastomotic bands of granulosa cells). Orientation of the cells about a central space (Call-Exner bodies) results in a characteristic follicular pattern. The tumor cells are typically spindle shaped and have a cleaved, elongated nucleus (coffee bean appearance). Three fourths of granulosa cell tumors are functional, means that they secrete estrogens. Consequently, endometrial hyperplasia is a common presenting sign. Hyperplasia may progress to endometrial adenocarcinoma, if the functioning granulosa cell tumor remains undetected.

Sertoli-Leydig cell tumor (arrhenoblastoma or androblastoma) is a rare mesenchymal neoplasm of the ovary of low malignant potential. It is the prototypical functional tumor associated with androgen secretion. It occurs at all ages but is most common in young women of child-bearing age.

Sertoli-Leydig cell tumors are unilateral and vary in size from microscopic foci to very large lesions, most measuring between 5 and 15 cm in diameter. They tend to form lobulated, solid, yellow or tan masses. Microscopically, the tumors vary from well differentiated to poorly differentiated, and some exhibit heterologous elements (papillae, glands, cartilage). The most characteristic features are large Leydig cells, which have abundant eosinophilic cytoplasm, and fine trabeculae of sex cords, which are immature solid tubules of embryonic Sertoli cells. Patients with functioning tumors (about half of them) present with signs of virilization, evidenced by hirsutism, deep voice. The initial signs of the tumor are often defeminization, manifested as breast atrophy, amenorrhea, and loss of hip fat. Both virilization and defeminization result from the secretion of testosterone and other androgenic hormones by the Sertoli-Leydig cell tumor.

Steroid cell tumors also known as “lipid / lipoid cell tumors” are composed of steroid-type cells resembling lutein cells, Leydig cells, and adrenal cortical cells. Most steroid cell tumors are hormonally active, usually with androgenic manifestations (some secrete testosterone as *hilus cell tumor,* whereas others synthesize weaker androgens)

4. Tumors metastatic to the ovary. About 3% of ovarian cancers arise outside the ovary, the most common primary sites being in descending order: breast, large intestine, stomach, and other genital organs. The tumors vary in size from microscopic lesions to large masses, bilateral ovarian involvement being an important clue to the diagnosis.

Krukenberg tumors are ovarian metastases in which the tumor appears as nests of mucin-filled “signet-ring” cells within a cellular stroma derived from the ovary. The stomach is the primary site in 75% of the cases, and most of other Krukenberg tumors are from the colon.

VI. BREAST PATHOLOGY

INFLAMMATORY DISEASES

Acute mastitis and abscess. Acute bacterial infection of the breast, bacterial mastitis, may be seen at any age, but by for the most frequent setting in the postpartum lactating or involuting breast. This disorder is usually secondary to obstruction of the duct system by inspisated secretions, with stasis of secretions. The most common organisms isolated are Staphylococcus and Streptococcus. As in other forms of acute inflammation, the infection may progress to abscess formation, a complication that necessitates surgical intervention.

Granulomatous mastitis.

Granulomatous mastitis is a rare condition in which the terminal duct lobular unit is the site of an intense granulomatous and chronic inflammatory process with conspicuous giant cells. It should properly be termed 'idiopathic' granulomatous mastitis because the aetiology is unknown.

Leakage from silicone breast implants used either for breast augmentation or as a breast reconstruction procedure after surgery for carcinoma is usually without harmful effect but may induce a granulomatous giant-cell reaction and cause tenderness or nodularity. Microscopically, fragments of the inert material is seen, surrounded by macrophages and multinucleated giant cells.

Sarcoidosis can be associated with scattered granulomas in the breast. Unlike the idiopathic granulomatous mastitis, the granulomas are not confined to lobular structures.

Tuberculosis of the breast is rare. It may arise by haematogenous, lymphatic, or direct spread, usually from the lungs or pleura. It may remain localized as a single caseating lesion, which sometimes discharges through the skin, or it may spread extensively through the breast.

Traumatic fat necrosis

Traumatic fat necrosis arises in the fatty tissue of the breast and may present as a hard lump mimicking cancer. It is caused by injury to the fat cells, although this may be relatively minor particularly in the obese or pendulous breast, and in many instances no history of trauma is obtained. The initial necrosis is accompanied by haemorrhage and followed by an acute inflammatory reaction. The lesion becomes heavily infiltrated by foamy macrophages containing lipid and often haemosiderin, and crystals of lipid may be deposited stimulating a foreign-body giant cell reaction. Granulation tissue forms around the lesion and gradually matures into a thick layer of fibrous tissue which often together with calcification, accounts for the presentation as a firm or hard lump.

BENIGN EPITHELIAL LESIONS

Benign epithelial lesions are classified into three groups, according to the subsequent risk of developing breast cancer:

(1) *nonproliferative breast changes* (fibrocystic change), lesions not associated with increased risk

2) *proliferative breast disease without (epithelial) atypia,* entails 1.5–2 fold increased risk of developing carcinoma over 5–15 years

(3) *proliferative breast lesions with (epithelial) atypia (atypical hyperplasia),* involve a greater relative risk (4–5 fold). Such patients require close clinical monitoring.

Nonproliferative breast change or **fibrocystic change** of the breast refers to a constellation of morphologic features characterized by:

- cystic dilatation of terminal ducts, often with apocrine metaplasia
- relative increase in fibrous stroma (fibrosis)
- variable proliferation of terminal duct epithelial elements (adenosis)

The cause of fibrocystic changes is unknown. Symptomatic fibrocystic change, in which large, clinically detectable cysts are formed, occur in 10% of adult women between the age of 35 and 55 years old. The frequency of both clinical and histologic fibrocystic change decreases progressively after the menopause.

The morphologic hallmarks of fibrocystic change are an increase in dense, fibrous stroma and some degree of cystic dilatation of the terminal ducts. Most often, cystic changes are minor. The large

cysts, up to 5 cm in diameter, often contain dark, thin fluid, which imparts a blue color to the unopened cysts.

On microscopic examination, the epithelium lining the *cysts* varies from columnar to flattened or may be entirely absent. A frequent change is an alteration of the epithelial lining, termed apocrine metaplasia. The metaplastic cells are larger and more eosinophilic than the cells that usually line the ducts and resemble apocrine sweat gland epithelium. These cells are usually arranged in a single layer, but on occasion they form papillary structures.

Cysts frequently rupture, releasing secretory material into the adjacent stroma. The resulting chronic inflammation and *fibrosis* contribute to the palpable nodularity of the breast.

Adenosis is defined as an increase in the number of acini per lobule. Calcifications are occasionally present within the lumens. The acini are lined by columnar cells, doubled by myoepithelial cell layer basally located.

Proliferative breast disease without atypia refers to one or more of several forms of epithelial proliferation that are not clonal, so are not commonly found to have genetic changes. Thus they are predictors of risk but unlikely to be true precursors of carcinoma. They are detected as mammographic densities, calcifications, or as incidental findings in biopsies performed for other reasons. Among these forms of epithelial proliferation are:

- **(usual) epithelial hyperplasia**: increased numbers of both luminal and myoepithelial cell types fill and distend ducts and lobules. There may be more than 4 cell layers, often bridging across duct lumens. Nuclei may be so oriented as to present a streaming pattern. Secondary spaces are slit-like, irregular and typically peripheral in location. Both luminal and basal epithelial cells proliferate.
- **sclerosing adenosis** shows disorderly proliferation of epithelial, myoepithelial and intralobular stromal cells, resulting in distortion and expansion of lobules and obliterating duct spaces. In cases that are difficult to distinguish from invasive carcinoma, immunohistochemistry can highlight the preservation of myoepithelial cells around distorted ducts. Lesions vary from microscopic foci to masses that may be palpable and that may be mistaken clinically and radiologically (because are often calcified) for carcinoma.
- **papilloma** grows within a dilated duct. Dilated duct spaces contain multiple branching papillae with fibrovascular cores. These are lined by a layer of myoepithelium, on which one or more layers (epithelial hyperplasia) of epithelium lie. Apocrine metaplasia is frequently present. Large duct papillomas (central papillomas) are situated in the lactiferous sinuses of the nipple and are usually solitary. Patients may present with a mass lesion or an often bloody nipple discharge. On mammography, central papillomas are well-circumscribed masses. Small duct papillomas (peripheral papillomas) are commonly multiple (papillomatosis) and located deeper within the ductal system - in terminal duct lobular units. Peripheral papillomas are identified often as clustered calcifications or small nodular masses.

Proliferative breast lesions with (epithelial) atypia = atypical hyperplasia: is a clonal proliferation having some, but not all, of the histologic features that are required for the diagnosis of carcinoma in situ.

- **atypical ductal hyperplasia (ADH)** is an intraductal epithelial proliferation with a dual population of low-grade neoplastic epithelial cells and benign cells. The benign population may comprise normal lining cells or proliferating cells showing epithelial hyperplasia of usual type. The neoplastic population consists of monomorphic small cells that are evenly spaced, with well-defined cytoplasmic borders and round, hyperchromatic, uniform nuclei. These form architecturally complex structures, such as micropapillae, rigid bridges, bars, solid sheets or cribriform arrays
- **atypical lobular hyperplasia (ALH)** consists of cells identical to those of lobular carcinoma *in situ* (monomorphic small, round, loosely cohesive cells), but the cells do not fill or distend more than 50% of the acini within a lobule. Is mostly an incidental finding.
- **flat epithelial atypia (FEA)** describes a lesion of TDLUs in which acini are variably dilated, lined by one or several layers of epithelial cells, with low-grade cytologic atypia. Cells show uniform round nuclei and a slight increase in the nuclear-to-cytoplasmic ratio.

Cell polarity is lost, and nucleoli are variably prominent. Architectural complexity (described with ADH) is absent.

Of note regarding the breast benign epithelial lesions

- Benign epithelial lesions usually do not cause symptoms but are frequently detected as mammographic calcifications or densities.
- These lesions are classified according to the subsequent risk of cancer in either breast.
- The majority are not precursors of cancer.
- Although risk reduction can be achieved by surgery or chemoprevention, the majority of women will not develop cancer and many women choose surveillance instead of intervention.

FIBROEPITHELIAL LESIONS arise from intralobular stroma and contain both stromal and epithelial elements. The specialized stroma may elaborate growth factors for epithelial cells, resulting in the proliferation of the epithelial component of these tumors.

Fibroadenoma. The most common benign neoplasm of the breast is the fibroadenoma, a tumor composed of epithelial and stromal elements that originates from the terminal duct lobular unit. Fibroadenomas usually are found in women between the ages of 20 and 35, although they also occur in adolescent girls. Fibroadenomas do not regress spontaneously; they commonly enlarge more rapidly during pregnancy and cease to grow after the menopause. Although they are hormonally responsive, a causal relationship between hormones and the development of fibroadenomas has not been established.

Fibroadenoma is a round, rubbery tumor, which is sharply demarcated from the surrounding breast and is thus freely movable. The cut surface appears glistening gray-white. Although it may vary in size from a microscopic lesion to a large tumor, it is usually 2 to 4 cm in diameter when first detected. On microscopic examination, fibroadenomas are distinctive, being composed of a mixture of fibrous connective tissue and ducts. The ducts may be either simple and round or elongate and branching, and are dispersed within a characteristic fibrous stroma. This fibrous tissue, which forms most of the tumor, often compresses the proliferated ducts, reducing them to curvilinear slits (the intracanalicular pattern). In other areas, the ducts remain patent because the stroma proliferates circumferentially around them (the pericanalicular pattern). These growth patterns don't have any prognostic importance. The fibrous stroma varies from loose and myxomatous to hyalinized collagen. The appearance of the epithelium ranges from the double layer of epithelium of normal lobules to varying degrees of hyperplasia.

Phyllodes tumor like fibroadenoma, arise from intralobular stroma, but is much less common. The tumor vary in size from a few centimeters to massive lesion involving the entire breast and is sharply circumscribed. Its cut surfaces is firm, glistening and grayish white. On microscopy, fronds of hypercellular stroma lead to formation of leaf-like structures, which project into cystic spaces. These spaces are lined by a dual layer of benign epithelium and myoepithelium. The stroma is mild or moderately hypercellular, with mild cytologic atypia and few mitoses.

MALIGNANT TUMORS.

Breast cancer is one of the most common malignancy of women and is second only to lung cancer as a cause of cancer deaths. The risk of death from breast cancer in those diagnosed with the disease remained constant for many years, but since 1994 has gradually declined from 30% to about 20%. This decrease is attributed to mammographic screening as well as more effective treatment modalities. Breast cancer is uncommon before the age of 25 years, but the incidence increases rapidly after age 30. A woman who lives to age 90 has a one in eight chance of developing breast cancer.

The pathogenesis of breast cancer is unknown, but a wealth of epidemiologic and clinical studies has implicated a number of factors that are associated with the risk of breast cancer:

1. hereditary factors:
    a. *germline mutations*: 5% to 10% of breast cancers occur in persons with germline mutations in tumor suppressor genes: BRCA1, BRCA2, TP53 and CHEK2. It is likely that complete loss-of-function of these proteins creates a "mutator" phenotype, an increased propensity to accumulate genetic damage that speeds cancer development

b. *first-degree relatives with breast cancer*. About 15% to 20% of women with breast cancer have an affected first degree relative (mother, sister or daughter), but do not carry an identified breast cancer gene mutation

2. age: breast cancer risk rises throughout a woman's life-time, peaking at 70 to 80 years and then declining slightly thereafter
3. hormonal status – cumulative lifetime exposure to estrogen: early menarche (younger than 11 years), late menopause, and older age at first-term pregnancy (after 35 years old), menopausal hormone therapy increase the risk
4. breast density: women with very dense breasts on mammography have 4-to 6-fold risk for breast cancer
5. benign breast disease: a prior breast biopsy revealing atypical hyperplasia or proliferative changes increases the risk of invasive carcinoma
6. radiation exposure: radiation to the chest, for cancer therapy (Hodgkin lymphoma for example)
7. other as diet, obesity, environmental toxins

Almost all (>95%) of breast malignancies are adenocarcinomas that first arise in the glandular epithelium of the terminal duct lobular unit as carcinoma in situ. At the time of clinical detection the majority (at least 70%) will have breached the basement membrane and invaded the stroma. Carcinoma in situ refers to a neoplastic proliferation of epithelial cells that is confined to ducts and lobules by the basement membrane. Invasive carcinoma (synonymous with "infiltrating" carcinoma) has penetrated through the basement membrane and grows within stroma. Here, the cells have the potential to invade into the vasculature and thereby reach regional lymph nodes and distant sites.

The terms *ductal* and *lobular* are used to describe subsets of both in situ and invasive carcinomas based on the resemblance of the involved space to normal ducts or lobules. It is now recognized that these growth patterns are not related to the cell of origin, because both arise from cells in the terminal duct lobular unit, but rather reflect differences in tumor cell genetics and biology.

1. Carcinoma in situ (noninvasive carcinoma) the preinvasive form of cancer, exhibits the histologic types: ductal carcinoma in situ and lobular carcinoma in situ.

a) *Ductal carcinoma in situ (DCIS)* arises in the terminal duct lobular unit which may become markedly enlarged, thereby resembling large ducts. By definition, DCIS is a malignant clonal proliferation of epithelial cells limited to ducts and lobules by the basement membrane, meaning that myoepithelial cells are preserved in the involved ducts / lobules.

DCIS is almost always detected by mammography (comprises 15% to 30% of carcinomas in screened populations, from 5% previously to imagistic surveillance of women over 40 years of age) as a result of calcifications associated with secretory material or necrosis.

Ductal carcinoma in situ has two main histologic variants: *comedo DCIS* (intraductal necrosis present, architectural growth of malignant cells: solid mainly) and *noncomedo DCIS* (no intraductal necrosis and various growth patterns for malignant cells: cribriform - regular fenestrations "cookie cuter-like", micropapillary - bulbous protrusions without a fibrovascular core, papillary - true papillae with fibrovascular cores that lack a myoepithelial cell layer, solid). Because multiple architectural patterns can coexist in one lesion, more important prognostically is the nuclear grade of the carcinoma cells: low (round, regular hyperchromatic nuclei, infrequent mitoses), intermediate and high-grade (irregular nuclei with prominent nucleoli and coarse chromatin, frequent mitoses).

As a conclusion to be remembered for DCIS diagnosis: the nuclear grade of malignant cells and the presence of necrosis are better predictors of local recurrence and progression to invasion than architectural type.

Comedo DCIS is composed of very large, pleomorphic cells, which have abundant eosinophilic cytoplasm and irregular nuclei, commonly with prominent nucleoli (nuclear high-grade). Comedo DCIS typically grows in a solid pattern and often becomes centrally necrotic (intraductal necrosis). On gross examination, the cut surface shows distended ducts containing pasty necrotic debris, resembling comedos, hence the term *comedo necrosis*. Even though the malignant cells do not invade through the

basement membrane of the ducts, this form of carcinoma in situ commonly incites a chronic inflammatory and fibroblastic response in the surrounding stroma.

Noncomedo DCIS tends to form papillary structures and small, regular fenestrations (cribriform pattern) rather than a solid growth. This tumor has cells and nuclei that are smaller and more regular (nuclear low-grade) than those of the comedo type. In contrast with comedo DCIS, it is less likely to incite a desmoplastic response in the surrounding tissue.

Breast conservation is appropriate for most women diagnosed with DCIS, but for cases with higher risk of recurrence and/or progression to invasive form (major factors being: high nuclear grade and necrosis, extent of disease, and positive surgical margins), the managenent includes postoperative radiation therapy and medication with selective estrogen receptors modulators (the latter for hormone receptor positive cases only).

b) *Lobular carcinoma in situ (LCIS)* is a clonal proliferation of cells within ducts and lobules that grow in a discohesive fashion, usually due to an acquired loss of the tumor suppressor protein **E-cadherin** (that contributes to the cohesion of normal epithelial cells in the breast).

The term "lobular" was used to describe this lesion because the cells expand but do not distort involved spaces and, thus, the underlying lobular architecture is preserved. LCIS is always an incidental biopsy finding, since it is not associated with calcifications or stromal reactions that produce mammographic densities. As a result, its incidence (1% to 6% of all carcinomas) did not increase after the introduction of mammographic screening. When both breasts are biopsied, LCIS is bilateral in 20% to 40% of cases, compared with 10% to 20% of cases of DCIS.

LCIS also arises in the terminal duct lobular unit; the cancer cells tend to be smaller and more monotonous than those of the ductal type, with round, regular nuclei and minute nucleoli. Lobular carcinoma in situ does not form papillary or cribriform structures. The malignant cells appear as solid clusters that pack and distend the terminal ducts, but not to the extent of in situ ductal carcinoma.

Necrosis and secretory activity are not seen with classic LCIS and, thus, substrates for calcification are not present. LCIS almost always expresses hormone receptors (ER and PR); the lack of E-cadherin expression results in a rounded shape of cells without attachment to adjacent cells. Lobular carcinoma in situ does not usually incite the dense fibrosis and chronic inflammation so characteristic of ductal carcinoma in situ.

LCIS is a risk factor for invasive carcinoma. Invasive carcinoma develops in 25% to 35% of women over 20 to 30 years time, similar to that observed for untreated DCIS. However, unlike DCIS, the risk is almost as high in the contralateral breast as in the ipsilateral breast. Treatment choices include bilateral prophylactic mastectomy, medication with selective estrogen receptors modulators (tamoxifen) or close clinical follow-up (with mammography included).

2. Invasive (infiltrating) carcinoma

Breast carcinomas have a wide variety of morphologic appearances. The mammographic and gross appearance of invasive carcinoma varies widely depending on the size of the tumor and on the stromal reaction elicites by the tumor:

- invasive carcinomas presenting on mammography as calcifications without an associated density are generally less than 1 cm in size. In the absence of mammographic screening, invasive carcinoma usually presents as a mass of at least 2 to 3 cm in size. They most commonly present as a hard, irregular radiodense mass associated with a desmoplastic stromal reaction. When cut or scraped, such tumors typically produce a characteristic grating sound due to small, central pinpoint foci or streaks of chalky-white desmoplastic stroma and occasional foci of calcification. Less commonly, tumors present as deceptively well-circumscribed masses composed of sheets of tumor cells with scant stromal reaction or may be almost imperceptible being comprised of scattered neoplastic glands or single tumor cells infiltrating otherwise unremarkable fibrofatty tissue.
- larger carcinomas may invade the pectoralis muscle and be fixed to the chest wall or invade into the dermis and cause dimpling of the skin. When the tumor involves the central portion of the breast, retraction of the nipple may develop.
- rarely, breast cancer presents as metastasis to an axillary node or distant metastasis before cancer is detected in the breast. In such cases, the primary carcinoma may be small, or be

obscured by dense breast tissue, or fail to produce a desmoplastic response, making it difficult to detect by palpation or mammography. In most cases, these "occult" primary tumors can be detected by imaging studies using ultrasound or MRI.

The microscopical appearance currently classify the invasive breast carcinomas into special histologic types (one third of cases) and "ductal" or no special type (NST) - the remainder group (two thirds of cases).

All types of invasive carcinoma are graded using the *Nottingham histologic score* (also called the modified Bloom and Richardson method) imparts points accordingly to tubule formation, nuclear pleomorphism, and mitotic rate. The added points (1 to 3 for each category) divide carcinomas into grade I (well differentiated), grade II (moderately differentiated), and grade III (poorly differentiated) types.

- **Grade I** carcinomas grow in a tubular pattern with small round nuclei and have a low proliferative rate.
- **Grade II** carcinomas may also show some tubule formation, but solid clusters or single infiltrating cells are also present. There is a greater degree of nuclear pleomorphism and mitotic figures are present.
- **Grade III** carcinomas invade as ragged nests or solid sheets of cells with enlarged irregular nuclei. A high proliferative rate and areas of tumor necrosis are common.

Ductal NST is the most common form of breast invasive carcinoma and presents as irregular, dense mass on mammography or ultrasound. It is usually moderately or poorly defined, nodular or stellate fixed mass, with firm to hard cut surfaces, which often is referred to as *scirrhous carcinoma.*

Tumor cells form trabeculae, sheets, nests and glands. Nuclear pleomorphism and mitotic counts vary. Surrounding stroma varies from desmoplastic to collagenous. Higher-grade lesions may show tumor necrosis. If a special-type component makes up over 50% of the tumor, the tumor is considered mixed (i.e., ductal with special-type features). DCIS is present in up to 80% of cases and is typically of the same nuclear grade as the invasive component.

Overall, 35%–50% of patients with ductal NST invasive carcinoma survive 10 years, varying according to grade, tumor and lymph node stage and the presence of lymphovascular invasion.

Special histologic types of invasive breast carcinoma:

- **Invasive lobular carcinoma** is the second most common form of invasive breast cancer, accounting for 5% – 15% of all invasive carcinomas. Because stromal desmoplasia and fibrosis may be minimal, patients often have clinically silent disease grossly and by mammography, or may present with a poorly defined thickening of the breast. Lobular cancers characteristically show discohesive malignant epithelial cells that infiltrate the stroma diffusely. They often line up in a row „Indian filling" and may show a periductal "targetoid" arrangement. They do not form ducts, but rather solid sheets, trabeculae or nests. These carcinomas tend to spread to the peritoneum, retroperitoneum, ovary and uterus, leptomeninges and gastrointestinal tract. Matched for grade and stage, their prognosis is similar to that of ductal NST cancers. *Signet ring cell carcinoma* is a rare variant of lobular carcinoma. Although the overall growth pattern is identical to that of the ordinary invasive lobular carcinoma, the small, regular tumor cells possess intracellular mucin. The mucin commonly compresses the nucleus to one side, giving the cell a "signet ring" appearance.
- **Tubular carcinoma** represent 1% – 2% of invasive breast cancers. Tubular carcinomas are well-defined stellate masses whose cellular composition is almost entirely round-open and angulated tubules, lined by a single layer of mildly atypical epithelial cells. Being a well-differentiated carcinoma, the prognosis, when it is not admixed with other types is excellent, and it is virtually always cured by mastectomy.
- **Mucinous / colloid carcinoma.** Patients with mucinous carcinoma are typically older than those with other tumor types. These tumors, which make up 1% – 6% of breast cancers, are well circumscribed, with a gelatinous texture. On cut section, colloid carcinoma has a glistening surface and mucoid consistency. Low-grade malignant epithelial cells form acini, nests or trabeculae, which appear to float in pools of extracellular mucin. Patients with pure

mucinous carcinoma have an excellent prognosis. However, colloid carcinoma is often admixed with infiltrating ductal NSTcarcinoma, in which circumstance the prognosis is determined by the ductal component.

- Classic **medullary carcinomas** are exceptionally rare, although other types of carcinoma may show *medullary features*. Almost 1/2 of patients are younger than 50. Medullary tumors are well circumscribed and soft, and include all of the following: (1) gross: circumscribed, pushing margins, which on mammography lacks calcifications (2) microsopically: high nuclear grade; syncytial growth pattern in more than 75% of the tumor; a moderate or marked lymphoplasmacytic infiltrate; and no tubule formation. The prognosis for pure medullary carcinoma is better than for high-grade ductal NST tumors, and lymph node metastases occur less frequently.
- Pure **micropapillary carcinoma** occurs rarely, but micropapillary areas are more often admixed with ductal NST carcinoma. In these tumors, malignant epithelial nests or acini are surrounded by a clear space, creating hollow balls of cells that float within intercellular fluid that mimic the appearance of true papillae. As micropapillary tumors invade lymphatic vessels and metastasize to lymph nodes readily, recognizing even a minor component of micropapillary carcinoma is important.
- **Papillary carcinoma**, as the name implies, produces true papillae, fronds of fibrovascular tissue lined by tumor cells.
- **Apocrine carcinoma** resemble the cells that line sweat glands. These cells have enlarged round nuclei with prominent nucleoli and abundant eosinophilic, occasionally granular, cytoplasm.
- **Metaplastic carcinomas** are heterogeneous tumors with malignant spindle cells, squamous cell carcinoma or heterologous elements, such as bone or cartilage.

Paget disease of the nipple is a rare manifestation of breast cancer (1% to 4% of cases) that presents as a unilateral erythematous eruption with a scale crust. Pruritus is common, and the lesion may be mistaken for eczema. Malignant cells (Paget cells) extend from DCIS within the ductal system via the lactiferous sinuses into nipple skin without crossing the basement membrane (an intraepithelial pattern of spreading / metastasizing). The tumor cells disrupt the normal epithelial barrier, allowing extracellular fluid to seep out onto the nipple surface. The Paget cells are readily detected by nipple biopsy or cytologic preparations of the exudate. A palpable mass is present in 50% to 60% of women with Paget disease, and almost all of these women have an underlying invasive carcinoma, usually poorly differentiated. In contrast, the remainder group of women without a palpable mass have only DCIS. Prognosis of Paget disease depends on the features of the underlying carcinoma.

For the last two decades with the advancement of molecular techniques, a new "taxonomy" began to develop in the classification of breast cancer: the "molecular" classification. Targeted therapies and more importantly, individualized treatment programs have become possible with the implementation of this classification.

Based on the expression of tumor cells for hormone / estrogen receptors, HER2 oncoprotein and their proliferative rate, breast cancers fall into three major **molecular subtypes**, each with important associations with clinical features, response to treatment, and outcome:

- **ER positive, HER2 negative (also termed "luminal,"** 50% to 65% of cancers**) is the most common form of invasive breast cancer.** Based on proliferation rates, it is further divided into two subgroups
    - **Luminal A: ER-positive, HER2-negative, low proliferation (40% to 55% of cancers): This group of breast cancers makes up the majority of cancers in older women and in men.** It is also the most common type detected by mammographic screening and in women treated with menopausal hormone therapy. The gene expression signature of this group of cancers is dominated by genes that are directly regulated by estrogen receptor. Many of these cancers are detected at an early stage. They have the lowest incidence of local recurrence and are often cured by surgery. When

these carcinomas do metastasize, it is often after a long period of time (over 5 years) and typically to bone. They respond well to hormonal treatment (which is standard for this subtype) and long survival with metastatic disease is possible.

- **Luminal B: ER positive, HER2 negative, high proliferation (approximately 10% of cancers):** Although these tumors are ER-positive, ER levels may be low and progesterone receptor expression may be low or absent. This is the most common type of carcinoma associated with *BRCA2* germline mutations. About 10% of these carcinomas show a complete response to chemotherapy

- **HER2 positive** (approximately 20% of cancers) **is the second most common molecular subtype of invasive breast cancer.** About half of these cancers are ER-positive. When present, ER expression is usually low; progesterone receptor expression is often absent. These cancers are relatively more common in young women, metastasize when small in size and early in the course, often to viscera and brain. Identification of cancers belonging to this subtype is achieved through assays of HER2 protein overexpression (immunohistochemistry method) or *HER2* gene amplification (molecular biology method: *in situ* hybridization). The introduction of trastuzumab (Herceptin), a humanized monoclonal antibody that specifically binds and inhibits HER2, markedly improved the outlook for patients with HER2 overexpressing cancers
- **ER negative, HER2 negative tumors ("basal-like" triple negative carcinoma;** approximately 15% of cancers**) are the third major molecular subtype.** These cancers are more common in young premenopausal women with *BRCA1* mutations. Due to high proliferation and rapid growth, this type of cancer is particularly likely to present as a palpable mass, metastasizes when small in size, frequently to viscera and to the brain. However, approximately 30% completely respond to chemotherapy and cure may be possible in this chemosensitive subgroup. Recurrences are generally diagnosed within 5 years of treatment. Local recurrence is common, even after mastectomy. Prolonged survival after distant metastasis is rare.

The correlations between the traditional old fashioned "morphological" classification and the new age "molecular" classification of breast carcinomas are:

- **ER positive, HER2 negative carcinoma.** Many morphologic patterns are possible, with grades ranging from well to poorly differentiated ductal NST carcinoma. Essentially all well differentiated NST carcinomas are in this group, as well as special histologic types: lobular, mucinous, tubular and papillary carcinomas.
- **HER2 positive carcinoma.** The majority of these carcinomas are poorly differentiated ductal NST with only a few classified as moderately differentiated. The special histologic types associated more often with this cell type are: apocrine and micropapillary carcinomas.
- **ER negative, HER2 negative carcinomas.** Almost all of these tumors are poorly differentiated ductal NST carcinoma (inclusive that with associated Paget disease of the nipple) and from special histologic types: medullary carcinoma, "carcinomas with medullary features", respectively some metaplastic carcinomas.

The outcome for women with breast cancer depends on the biologic features of the carcinoma (molecular or histologic type) and the extent to which the cancer has spread (stage) at the time of diagnosis. Many women with breast cancer have a normal life expectancy, whereas others have only a 10% chance of being alive in 5 years.

Prognostic factors fall into two groups — those related to the extent of carcinoma (tumor burden or stage) and those related to the underlying biology of the cancer.

Prognostic factors related to extent of carcinoma are as follows:

- ***Invasive carcinoma versus carcinoma in situ.*** Women with in situ carcinoma understandably have an excellent prognosis

- ***Distant metastases.*** Once distant metastases are present cure is unlikely, although long-term remissions and palliation can be achieved, especially in women with ER-positive tumors.
- ***Lymph node metastases.*** Axillary lymph node status is the most important prognostic factor for invasive carcinoma in the absence of distant metastases. With no nodal involvement, the 10-year disease-free survival rate is close to 70% to 80%; the rate falls to 35% to 40% with one to three positive nodes, and to 10% to 15% when more than 10 nodes are positive.
- ***Sentinel lymph node biopsy*** reduces the risk of postoperative morbidity (lymphedema, nerve damage of the corresponding arm) associated with axillary dissection, but if it is positive for carcinoma metastases, the procedure of axillary lymphadenectomy cannot be avoided.
- ***Lymphovascular invasion.*** Tumor cells are present within vascular spaces (either lymphatics or small capillaries) in about half of all invasive carcinomas. This finding is strongly associated with the presence of lymph node metastases.
- ***Tumor size.*** The risk of axillary lymph node metastases increases with the size of the primary tumor, but both are independent prognostic factors. Women with node-negative carcinomas less than 1 cm in size have a 10-year survival rate of more than 90%, whereas survival drops to 77% for cancers greater than 2 cm.
- ***Locally advanced disease.*** Carcinomas invading into skin or skeletal muscle are usually large and may be difficult to treat surgically.

Tumor size for pathologic staging system (TNM) for breast carcinomas:

pTis Carcinoma in situ (ductal or lobar) or Paget disease without invasive carcinoma
pT1a Invasive tumor >1 mm but ≤5 mm
pT1b Invasive tumor >5 mm but ≤1 cm
pT1c Invasive tumor >1 cm but ≤2 cm
pT2 Invasive tumor >2 cm but ≤5 cm
pT3 Invasive tumor >5 cm
pT4 Edema or tumor ulcerating through skin or satellite skin nodules and/or chest wall invasion

Other prognostic factors are related to tumor biology, as follows:

- **Molecular subtypes and histologic grade:** *Luminal A* tumors are typically low grade and have an excellent prognosis. *Luminal B* are of higher grade than are luminal A tumors and have a poorer prognosis. Tumors that *overexpress HER2* behave aggressively, but targeting HER2 with an antibody, trastuzumab, has significantly increased patient longevity. *Basal-like cancers* are highly aggressive with the poorest prognosis.
- **Special histologic types:** The survival rate of women with some special types of invasive carcinomas (tubular, mucinous, lobular, papillary) is greater than that of women with cancers of no special type.
- **Hormone status** Strongly ER-positive cancers are less likely to respond to chemotherapy. Conversely, cancers that fail to express either ER or PR are more likely to respond to chemotherapy.

Breast-conserving surgery (lumpectomy or quadrantectomy) is often used. Wider excision may be needed in patients with bulky disease. As indicated above, sentinel lymph node sampling often replaces (when negative for metastases) more extensive axillary lymph node chain removal. Postoperative radiation therapy is commonly used as well. Systemic therapies (hormonal, chemotherapy and targeted molecular modalities) are considered essential in managing patients with breast cancer.