Breast development and morphology

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INTRODUCTION

The breast undergoes dramatic changes in size, shape, and function in association with puberty, pregnancy, lactation, and menopause. It is also the origin of the most common malignancy in women [1]. The risk of developing breast cancer has been linked to both endogenous (eg, nulliparity, early menarche, older age at first pregnancy) and exogenous hormonal influences [2-5]. (See "Factors that modify breast cancer risk in women" and "Menopausal hormone therapy: Benefits and risks".)

The molecular mechanisms underlying the development of breast cancer, particularly estrogen-associated breast carcinogenesis, are incompletely understood. Increasing evidence points to developmental differences in the breast that may influence the risk of developing cancer. Thus, an understanding of breast development and morphology, and the biochemical factors that influence it, is pertinent to the study of both premalignant and malignant conditions affecting the breast.

ANATOMY

Gross anatomy — The mature adult breast lies between the second and sixth ribs in the vertical axis and between the sternal edge and the midaxillary line in the horizontal axis. Breast tissue also projects into the axilla as the axillary tail of Spence.

The breast comprises three major structures: skin, subcutaneous tissue, and breast tissue, which is composed of both epithelial and stromal elements. The epithelial components are branching ducts that connect the structural and functional units of the breast (the lobules) to

the nipple. The stroma, which comprises the majority of the breast volume in the nonlactating state, is composed of adipose and fibrous connective tissue.

The skin of the breast is thin and contains hair follicles, sebaceous glands, and exocrine sweat glands.

The nipple and areola have distinctive and specialized structures that make them easily identified from their histologic appearance. The nipple has abundant sensory nerve endings and sebaceous and apocrine sweat glands but not hair follicles. The stroma consists of dense collagen enriched in smooth muscle tissue, which can give rise to leiomyomas in this location (picture 1). The areola is more or less circular and pigmented, measuring 15 to 60 mm in diameter. The Montgomery (also known as Morgagni) tubercles, which are located near the periphery of the areola, are elevations formed by the openings of the sebaceous glands, also known as Montgomery glands.

The ducts from the breast parenchyma converge at the nipple and expand to form the lactiferous sinus. The lactiferous sinus communicates with the surface of the nipple via the collecting duct. The proximal portion of the collecting duct is similar to the remainder of the duct system, but the superficial portion (ie, toward the nipple orifice) is lined by squamous epithelium that can extend into the terminal portion of the lactiferous duct. The squamocolumnar junction is the area where the squamous epithelium meets the glandular epithelium, which is abrupt. Extension of the squamous epithelium into and beyond the lactiferous sinus is pathological, a condition referred to as squamous metaplasia, resulting in obstruction of the duct system.

The superficial pectoral fascia envelops the breast and is continuous with the superficial abdominal fascia (of Camper). The undersurface of the breast lies on the deep pectoral fascia, covering the pectoralis major and serratus anterior muscles. Connecting these two fascial layers are fibrous bands (the Cooper suspensory ligaments) that represent a natural means of support for the breast. The deep surface is macroscopically well demarcated; however, microscopic breast glandular elements can extend into and even beyond the deep fascial plane. Therefore, total mastectomy may not result in the removal of all the glandular tissue.

Histology — Microscopically, the breast tissue is comprised of epithelial and mesenchymal elements. The epithelial portion comprises secretory parts called acini that connect to a series of ducts that increase in diameter as they approach the nipple.

The terminal ductal lobular unit (TDLU) is the functional and structural unit of the breast. The TDLU comprises the distal smallest ducts (terminal duct) and the acini attached to them (picture 2). The epithelial elements of the TDLU, the acini and terminal duct, are embedded in the intralobular stroma, which is highly specialized and more cellular and

hormonally responsive compared with the interlobular stroma, which is comparatively fibrous and hormonally less sensitive. Knowledge of the structure of the periductal and lobular stroma is important in the understanding of the many disease processes. Most of the proliferative lesions as well as neoplastic lesions in the breast are derived from the TDLU.

A key feature vital to the understanding of the pathological changes in the breast is the specialized two-cell-type lining of the entire duct and lobular system. Under the light microscope, the two cell layers are clearly discernable, with the columnar or cuboidal larger and taller cells lining the luminal aspect of the duct and acini with an outer cell layer composed of the smaller, spindle-shaped myoepithelial cell layer, which lies between the epithelial cell layer and the basal lamina. The myoepithelial cell layer is continuous and lies parallel to the long axis of the duct system. The contractile properties of the myoepithelial cells contribute to the flow of milk during lactation.

Appreciation of the two-cell-type layer is critical in distinguishing benign from malignant processes. For example, in sclerosing adenosis and nipple adenomas, which are benign lesions, the two-cell layer is evident by routine histologic examination or ancillary immunohistochemical stains to detect the presence of the myoepithelial cell layer (picture 3). By contrast, in well-differentiated malignancies like tubular carcinoma, the myoepithelial cell layer is lost around invasive glands and confirms the malignant nature of these lesions, which can at times be challenging by morphology alone (picture 4) [6-8].

Blood supply and lymphatic drainage — The principal blood supply of the breast is derived from the internal mammary artery. Approximately one-third of the blood supply (mainly to the upper outer quadrant) is provided by the lateral thoracic arteries.

The lymphatic drainage of the breast is through both superficial (subepithelial and subdermal) and deep lymphatic vessels, and the lymph flows unidirectionally from the superficial to the deep plexus. Lymph flow from the deep subcutaneous and intramammary vessels moves centrifugally toward the axillary, internal mammary (IM), and clavicular lymph nodes. While most areas of the breast drain to the axillary nodes, drainage can also flow simultaneously or solely to the other nodal sites [9]. Initial studies estimated that approximately 3 percent of the lymph from the breast drains to the IM chain, whereas 97 percent flows to the axillary nodes [9]. However, a 1972 study using intraparenchymal radioactive gold injections in women without breast cancer found drainage to the IM nodes occurred in 36 percent overall [10].

Lymphatic mapping in patients with breast cancer has delineated drainage patterns for palpable and nonpalpable lesions. In a retrospective study that included 678 breast cancer patients with nodes visualized following lymphoscintigraphy, all palpable and nonpalpable centrally located lesions (n = 59) drained to the axillary lymph nodes [11]. However,

approximately 35 percent of the lesions also drained to the IM and/or clavicular chain. Most breast lesions (palpable and nonpalpable) from all quadrants drain to the axillary nodes.

Drainage to the axillary lymph nodes based upon location of the lesion includes:

- Upper outer quadrant (n = 336) – 95.8 percent
- Lower outer quadrant (n = 88) – 97.7 percent
- Upper inner quadrant (n = 145) – 93.1 percent
- Lower inner quadrant (n = 50) – 88.0 percent

Lesions in the inner quadrants of the breast were significantly more likely to drain to IM lymph nodes compared with lesions in the outer quadrants (37.4 versus 14.4 percent) [11]. Drainage to the IM lymph nodes based upon location of the lesion includes:

- Upper outer quadrant – 10.4 percent
- Lower outer quadrant – 29.5 percent
- Upper inner quadrant – 32.4 percent
- Lower inner quadrant – 52.0 percent

Largely for the purpose of determining metastatic progression in breast cancer, axillary lymph nodes are grouped by anatomic location and often described by dividing them into arbitrary levels. Level I lymph nodes lie lateral to the lateral border of the pectoralis minor muscle, level II nodes lie behind the pectoralis minor muscle, and level III nodes are located medial to the medial border of the pectoralis minor muscle.

The IM lymph nodes lie within extrapleural fat in the intercostal spaces in close proximity to the IM vessels. Like the axillary nodes, the IM nodes receive lymph drainage from all quadrants of the breast [12]. The number of lymph nodes described in the IM chain is variable. Nodes can extend from the fifth intercostal space to the retroclavicular region, but the most prevalent ones are in the upper three interspaces (figure 1).

NORMAL DEVELOPMENT

Human breast development is a progressive process that is initiated during embryonic life (picture 5). The breasts develop from ventral epidermal ridges (milk line), which appear in a five-week embryo and extend from the axilla to the upper medial thigh (figure 2). In humans only the extreme ends of this ridge, in the axilla or vulva, persist. The nipple is

formed by evagination of the mammary pit. Failure of this process leads to a congenitally inverted nipple.

At birth, the breast rudiment is formed by 10 to 12 primitive ductal elements located beneath the nipple-areolar complex. In the prepubertal years, these ducts exhibit relatively slow but steady growth and branching, with canalization into ductal structures. In boys, breast development ceases at this stage.

Although puberty marks the beginning of glandular maturation, full breast differentiation is attained only with subsequent pregnancy and lactation.

Pubertal changes — In girls, puberty usually begins around age 10 to 12 under the influence of hypothalamic gonadotropin-releasing hormone (see "Physiology of gonadotropin-releasing hormone"). The cells of the anterior pituitary gland release follicle-stimulating hormone (FSH) and luteinizing hormone (LH), which promote maturation of the ovarian follicles and their secretion of estrogens, primarily in the form of 17-beta estradiol. (See "Molecular biology and physiology of estrogen action".)

Breast development from puberty to adulthood is defined by several parameters, including external appearance, volume, number of structures present in the mammary gland, and the degree of branching or differentiation of the individual structures (picture 1 and figure 3) [3]. The external appearance of the breast from childhood to maturity has been divided into five phases by Tanner (picture 6). (See "Normal puberty".)

Lobule formation — From a microanatomic standpoint, puberty is marked by increased growth and branching of the ducts to form club-shaped terminal end buds; this is accompanied by an increase in the stromal component [3]. Growing terminal end buds form new branches, twigs, and small ductules (termed alveolar buds). We use the term alveolar bud to identify those structures that are morphologically more developed than the terminal end bud but more primitive than the terminal structure of the mature resting breast, the acinus. With further branching, alveolar buds become smaller and more numerous, and then they are called ductules.

Type 1 lobules — When an average of 11 alveolar buds/ductules cluster around a terminal duct, they form the type 1 lobule (picture 7).

Lobule formation is apparent within one to two years after the onset of the menses. Thereafter, glandular development is variable. Full differentiation of the mammary gland to its maximal degree of branching and secretory activity is a gradual process that takes many years (picture 8); it may never be attained if pregnancy does not supervene.

Type 2 and 3 lobules — The breast tissue of adult women contains two other identifiable types of lobules in addition to the type 1 lobule. The changing levels of estrogen and

progesterone during menstrual cycles stimulate the type 1 lobule to sprout new alveolar buds and gradually evolve to more mature structures called type 2 and type 3 lobules (picture 9 and picture 10). The number of alveolar buds per lobule increases from approximately 11 in the type 1 lobule to 47 in type 2 lobule and 80 in the type 3 lobule, respectively (table 1).

Parity and age both influence breast architecture [3,13]. The breasts of nulliparous women contain more undifferentiated structures, such as terminal ducts and type 1 lobules (65 to 80 percent of the total lobular component), with only occasional type 2 and 3 lobules. In contrast, the predominant structure in the breast of parous premenopausal women is the most differentiated type 3 lobule (70 to 90 percent of all lobules). By the end of the 40s, the breasts of both nulliparous and parous women are architecturally similar, containing predominantly type 1 lobules. However, they differ markedly with regard to cell kinetics and biologic behavior. In parous women, a first full-term pregnancy between the ages of 14 and 20 correlates with a significant increase in the number of type 3 lobules that predominate until the age of 40, after which a decrease in the number of type 3 lobules occurs [3]. This fact may provide some explanation as to the protective effects of an early first pregnancy on the risk of breast cancer. (See 'Menopause' below.)

Type 4 lobules — Progression from type 3 to type 4 lobules is attained during pregnancy. (See 'Early pregnancy' below.)

Menstrual cycle-related histologic changes — Both epithelial and stromal components of the terminal ductal lobular unit (TDLU) undergo histologic changes with the menstrual cycle. These changes are variable among the lobules. During the follicular phase, the epithelium lining the lobules (luminal cells) is small and cuboidal in shape and does not display secretory or mitotic activity. The intralobular stromal tissue is dense and hypocellular. In the luteal phase, the acini are open and enlarged due to luminal secretions. The intralobular stroma is loose, edematous, and more cellular than in the follicular phase.

Pregnancy and lactation — The pregnant woman undergoes anatomic and physiologic changes in almost every organ system. During this time, the maximum branching capability of the breast is expressed, and the secretory acinus that is formed during pregnancy represents a terminal outgrowth that marks the full extent of glandular differentiation. Fully differentiated secretory cells are characterized by their ability to synthesize and secrete milk proteins (caseins) and lipids (picture 11).

During pregnancy, the breast attains its maximum development in two distinct phases, characteristic of the early and late stages of pregnancy. Ductular sprouting predominates in the first trimester, while lobular formation exceeds ductal sprouting in the second trimester.

Early pregnancy — Under the influence of chorionic gonadotropin, many secretory glands develop from each bud, forming the type 3 lobule. Further proliferation of the distal elements of the ductal tree marks the progression from a type 3 lobule to a type 4 lobule (picture 12). In these newly formed lobules, the epithelial cells composing each acinus not only increase greatly in number due to active cell division but also increase in size, mainly because of cytoplasmic enlargement [3].

In mid-pregnancy, the lobules further enlarge and increase in number. They surround the duct from which their central branch proceeds so thickly that the chief duct, the terminal or intralobular terminal duct, can no longer be recognized. The transition between the terminal ducts and the budding acini is gradual, making the histologic distinction between the two of them difficult; both show evidence of early secretory activity.

Later pregnancy — Mammary changes during the second half of pregnancy are chiefly a continuation and accentuation of secretory activity. Further progressive branching continues with less prominent bud formation. The formation of fully differentiated secretory units or acini becomes increasingly evident. Proliferation of new acini is reduced, and the lumen of already formed units becomes distended by the accumulation of secretory material or colostrum.

Just before and during parturition, there is a new wave of mitotic activity within the mammary gland. At this time, and during lactation, the process of further growth and differentiation may be observed in the same lobule type, side by side with the process of milk secretion [3]. At this point, the glandular component of the breast has increased to the point where the breast is composed primarily of epithelial elements, with very little stroma. These changes persist throughout lactation.

Lobular involution (regression)

Postlactation — The postlactational breast requires a combination of lactogenic hormone deprivation and local signals to undergo glandular involution (regression or atrophy), a process characterized by apoptotic cell death and tissue remodeling. The factors that trigger apoptosis have not been clearly defined. Certain gene products are upregulated during mammary involution, as are local extracellular proteases that are involved in tissue remodeling [14,15].

Menopause — Menopause supervenes as a consequence of ovarian follicular atresia, resulting in an ovary completely devoid of follicles. This is characterized clinically by the absence of ovarian estradiol and progesterone secretion, resulting in amenorrhea. (See "Ovarian development and failure (menopause) in normal women".)

After menopause, the breast undergoes regression, with atrophy of the glandular elements and a marked decrease in the number of lobules (picture 13). This process differs greatly

from postlactational involution (regression or atrophy). In some areas, the lobules disappear completely, and only the ducts remain. Concurrently, the fibrous connective tissue component of the stroma decreases, and adipose tissue accumulates (picture 14).

Microanatomically, involution is manifested by an increasing number of type 1 lobules and a concomitant decline in the number of type 2 and 3 lobules, which, although more marked in parous women, also occurs in nulliparous women [3,13].

Adult male breast — Like the female breast, the adult male breast consists of epithelial and mesenchymal tissue. However, the epithelial component is limited to only ducts. No secretory portions including TDLU/acini are identified. The ducts are embedded in usually denser fibrous tissue.

ABNORMALITIES IN BREAST DEVELOPMENT

Congenital — The most common congenital abnormality of breast development, which can be seen in both sexes, is an accessory or supernumerary nipple (polythelia). The incidence in one study in neonates revealed ectopic or supernumerary nipples in 49 of 2035 infants (2.4 percent) [16]. Ectopic nipple tissue may occur at any point along the milk streak from the axilla to the groin. Rarely, accessory true mammary glands develop with a complete nipple-areolar complex, most commonly in the axilla (polymastia) [17]. During pregnancy and lactation, an accessory breast may swell, and if an associated nipple is present, it may secrete milk.

However, polythelia warrants attention for more than cosmesis alone [18]. Supernumerary nipples have been associated with an increased risk of genitourinary abnormalities, malignancies, segmentation defect of the vertebrae, Becker's nevus, and other developmental abnormalities [19-23].

Rare anomalies of the breast include [24,25]:

- Hypoplasia – Underdevelopment of the breast
- Amastia – Congenital absence of the breast
- Amazia – Absence of breast tissue, but a normal nipple-areolar complex is present

Unilateral hypoplasia may be accompanied by a normal, hypoplastic, or hyperplastic contralateral breast. Amazia usually presents as a component of a development syndrome and can be diagnosed during infancy or at the beginning of puberty [24]. These anomalies are amenable to reconstructive procedures [25-28].

The most severe of these deformities, amastia or severe unilateral hypoplasia, is associated with hypoplasia of the pectoral muscle in 90 percent of cases. However, the reverse does not

apply; in women with pectoral muscle abnormalities, 92 percent have a normal breast [29]. In Poland syndrome, abnormalities ranging from unilateral hypoplasia to absence of the breast and pectoral muscle frequently occur in combination with distal hypoplasia of the upper limb and anomalies of the hand (syndactyly, brachydactyly, oligodactyly) [26,30-32]. These anomalies may result from diminished blood flow in the subclavian artery during early fetal development. (See "Chest wall diseases and restrictive physiology".)

Premature thelarche — Premature thelarche is unilateral or bilateral discoid subareolar thickening without any other clinical evidence of sexual maturation prior to puberty. It can occur due to environmental factors or in the setting of *GNAS* gene mutation. The nodular breast tissue regresses in >50 percent of cases, especially if it started at <2 years of age. There is no predisposition to breast carcinoma, and most have normal menarche. Excision is contraindicated because this results in amastia. Histologically, the breast tissue resembles gynecomastoid hyperplasia. Early breast development in girls (premature thelarche) is also discussed separately. (See "Definition, etiology, and evaluation of precocious puberty".)

Juvenile hypertrophy — Juvenile hypertrophy is the rapid enlargement of one or both (frequent) breasts in adolescent girls. This is a benign process and should not be confused with neoplastic lesions. Reduction mammoplasty is the treatment. Histologic findings mirror changes seen in gynecomastia. Proliferating ducts show minimal lobule formation.

Acquired — The most common and avoidable cause of amazia is iatrogenic: the injudicious biopsy of a precociously developing breast. The use of radiation therapy in prepubertal girls to treat either hemangioma of the breast or intrathoracic disease can also result in amazia. Deformity may also develop in cases of traumatic injury of the developing breast. Macromastia is a rare condition in which massive enlargement occurs in a unilateral breast in women without obesity [33]. A mammoplasty can be performed to achieve symmetry with the contralateral breast.

HORMONAL INFLUENCES ON BREAST DEVELOPMENT

Normal mammary growth, differentiation, and regression are the result of complex interactions between systemic hormones and local cell-cell interactions, which are mediated by a variety of growth factors, including epidermal growth factor, transforming growth factor, and fibroblast growth factor. The morphologic response of the mammary gland to these complex interactions results in developmental changes that permanently modify both its architecture and biologic characteristics [34,35].

Estrogens and progesterone — The breast epithelial lining cells express estrogen receptor (ER). The ER-alpha expression is seen in the nuclei of ductal and lobular cells (lobules more than ducts), which are variable and identified in scattered cells as weak-to-moderate intensity

by immunohistochemistry. The ER-beta (second form of ER) expression is noted in the epithelium as well as the nuclei of stromal cells. The progesterone expression is noted in normal breast ductal and lobular cell nuclei, with an expression pattern similar to that of ER-alpha.

Estrogens are considered to play the major role in promoting proliferation of the breast epithelium. Estradiol acts locally on the mammary gland, stimulating DNA synthesis and promoting bud formation [34]. These biologic activities are thought to be predominantly mediated by ER alpha, which activates transcription of specific genes containing the estrogen response elements [36]. The importance of ER-alpha is reflected in the poorly developed mammary glands of knockout mice who are ER-alpha (but not ER-beta)-null [37].

Normal ductal development requires both estrogen and progesterone. Progesterone acts in conjunction with estrogen to regulate breast development through its specific receptor (PR) on breast epithelial cells. As evidence of the importance of progesterone, during the normal menstrual cycle, the breast epithelium does not exhibit maximal proliferation during the follicular phase, when estrogen secretion is at its peak, but instead during the luteal phase, when progesterone levels are at their highest and estrogen levels have begun to decline. (See "Normal menstrual cycle".)

Cell proliferation and hormone receptors — The proliferative activity of the mammary epithelium varies with the degree of lobular differentiation. In humans, the highest level of proliferative activity is observed in the undifferentiated type 1 lobule, present in the breast of young nulliparous females [13,34,35,38]. With progressive differentiation into type 2 and 3 lobules under the hormonal influences of the menstrual cycle, there is a concomitant reduction in proliferative activity. Compared with the cells comprising type 1 lobules, the rate of cellular proliferation, as determined by the percentage of cells that stain positively with Ki-67, is decreased threefold in the type 2 lobules and 10-fold in the type 3 lobules (table 2) [35,39].

The content of ER-alpha and PR in the lobular structures of the breast is directly proportional to the rate of cellular proliferation [39]. Type 1 lobules consistently contain a higher percentage of ER- and PR-positive cells than do type 2 or 3 lobules, indicating a progressive decease in the number of receptor-positive cells as the structures become more differentiated (table 2).

These biologic differences may have profound implications for cancer risk. The fact that the highest proliferative capacity and the highest percentage of ER-alpha- and PR-positive cells are present in type 1 lobules provides a mechanistic explanation for the greater susceptibility of these structures to be transformed by chemical carcinogens in vitro and in experimental animals [2,40-46] and supports the observation that type 1 lobules are the site of origin of ductal carcinomas (see 'Cancer risk' below). The proliferating cells differ from those that are

receptor positive, suggesting that the proliferative influence of estrogen on the breast epithelium is indirect [39].

PARITY, LOBULAR DIFFERENTIATION, AND BREAST CANCER RISK

By the end of the fifth decade, the breast of both nulliparous and parous women is composed predominantly of type 1 lobules [13]. However, despite their architectural similarity, there are important differences between the type 1 lobules of the nulliparous woman and the regressed type 1 lobules of the parous woman. Type 1 lobules of nulliparous women have a very active intralobular stroma, whereas those of the parous woman are more hyalinized and indicative of a regressed structure (picture 13). Another important difference is the higher proliferative activity in the type 1 lobules of nulliparous compared with parous women. The cells of both type 1 and type 3 lobules in the parous breast are predominantly in the G0 phase or resting phase, while in type 1 lobules of the nulliparous breast, proliferating cells predominate and the fraction of cells in G0 is quite low. Thus, parity, in addition to exerting an important influence on the lobular composition of the breast, profoundly influences its proliferative activity.

These biologic differences may provide some explanation for the increased susceptibility of the breast of nulliparous women to develop breast cancer. It is hypothesized that unlike parous women, the type 1 lobule found in the breast of nulliparous women never went through the process of differentiation, seldom reaching the type 3 lobule, and never the type 4 stages [13]. Although the lobules of parous women regress at menopause to type 1, they are permanently genetically imprinted by the differentiation process in some way that protects them from neoplastic transformation, even though these changes are no longer morphologically observable. Thus, they are biologically different from the type 1 lobule of nulliparous women.

The postulated mechanism of protection conferred by early full-term pregnancy is that the degree of differentiation acquired through early pregnancy changes the "genomic signature" that differentiates the type 1 lobule from the early parous women from that of the nulliparous women by shifting the stem cell population from "stem cell 1" to "stem cell 2." The genomic signature of the stem cell 2 differs from that of the stem cell 1 cells, and the specific gene products synthesized by the stem cell 2 population can be detected in the blood after the pregnancy event is over [47-49]. Detection of these gene products in circulating blood indicates that the breast has completed the process of differentiation, thus serving as an indicator of the presence of a protective factor, namely, a surrogate marker of lower susceptibility to develop cancer in early parous women. The pattern of gene expression of the stem cell 2 could potentially be used as useful intermediate end points for

evaluating the degree of mammary gland differentiation and for evaluating preventive agents like human chorionic gonadotropin.

The extent of age-related menopausal involution (regression or atrophy) of the type 1 lobule appears to influence the risk of breast cancer and may modify other breast cancer risk factors, including parity. It has also been postulated that unresponsive lobules that fail to undergo differentiation under the stimulus of pregnancy and lactation are responsible for cancer development despite the parity history [49-51].

Support for these observations was provided in a report that focused on breast biopsy specimens from 8736 women with benign breast disease [52]. The authors characterized the degree of involution (regression) of both the terminal duct lobular units (type 1 lobules) and the atrophic or involuted structures that result from the normal process of aging in the human breast. They defined complete involution as ≥75 percent of the lobules involuted, partial involution as 1 to 74 percent involuted, and none as 0 percent involuted. The relative risk of breast cancer was estimated based upon standardized incidence ratios by dividing the observed numbers of incident breast cancers by expected values of population-based incident breast cancers from the Iowa Surveillance, Epidemiology, and End Results (SEER) registry.

The following findings were noted:

The risk of breast cancer was significantly higher for women with no involution, compared with those with partial or complete involution (relative risks [RRs] 1.88, 1.47, and 0.91, respectively).

- The degree of involution modified the risk of developing breast cancer in women who had atypia in their breast biopsies (RR 7.79, 4.06, and 1.49 for women with no, partial, and complete involution, respectively) as well as for those with proliferative disease without atypia (RR 2.94 and 1.11 for those with no and complete involution, respectively).

- There was an interaction with family history as well; women with weak or no family history of breast cancer who had complete involution had a risk for breast cancer that was fivefold lower than the risk of those with a strong family history and no involution (RR 0.59 versus 2.77, respectively).

- Among nulliparous women and those whose age at first birth was over the age of 30, the absence of involution significantly increased the risk of breast cancer (RR 2.41 versus 2.74, respectively). In contrast, for both groups, there was no excess risk if involution was complete.

Subsequent studies confirm that the degree of lobular involution is inversely associated with breast cancer risk [53,54]. A nested case-control study of lobule involution used the number of acini per lobule as a reflection of the degree of involution and compared acinar counts in women who did or did not go on to develop breast cancer [53]. Women with no involution had a higher mean acinar count (32 acini/lobule) than women with partial (19.7 acini/lobule) or complete involution (7.7 acini/lobule). There was a stepwise increase in breast cancer risk with increasing numbers of acini and decreasing degree of involution per lobule. Another study assessed lobule type rather than the degree of involution but arrived at a similar conclusion: women with more type 1 lobules, with more complete involution, have a lower breast cancer risk [53].

Taken together, these data suggest that breast cancer risk is decreased in women with more type 1 lobules and more complete involution (regression) of lobular structures. This reflects parity and terminal differentiation of lobules and helps to explain why pregnancy and lactation seem to decrease the risk of breast cancer [50]. These data also raise concerns that reactivation of type 1 lobules, as has been described in women receiving postmenopausal hormone therapy who develop dense breasts, may increase the risk of developing breast cancer [55].

ARCHITECTURAL PATTERNS AND BREAST PATHOLOGY

The fact that the mature breast exhibits variations in development, proliferative activity, and hormone receptor content raises the question of whether benign, premalignant, and/or malignant breast lesions develop as a reflection of these variations. A clinical overview of benign, high-risk, and malignant breast lesions is presented elsewhere. (See "Overview of benign breast diseases" and "Breast cysts: Clinical manifestations, diagnosis, and management" and "Atypia and lobular carcinoma in situ: High-risk lesions of the breast" and "Pathology of breast cancer".)

Proliferative lesions — The degree of breast development appears to be important in the susceptibility to proliferative influences [56]. One study compared the pattern of lobular development in breast tissues devoid of mammary pathology (33 reduction mammoplasties performed in both parous and nulliparous women) with that of 45 noncancerous breast biopsies performed because of mammographic abnormalities or clinically suspicious findings [56]. The patient populations were then subdivided according to parity status. Despite the absence of cancer, tissues obtained from breast biopsies had an architectural pattern that differed markedly from those obtained from reduction mammoplasties for women of comparable parity status. Parous women who underwent a breast biopsy had a significantly higher percentage of type 1 lobules (65 versus 17 percent) and a lower

percentage of type 3 lobules (14 versus 48 percent) than did the parous population of the reduction mammoplasty group.

When the groups were subdivided according to histologic diagnosis (21 normal breast, 15 ductal hyperplasia [DH], four with blunt duct adenosis [BDA; also called columnar cell change], and five with sclerosing adenosis [SAD]) and the tissues analyzed for lobular architecture, lesion type, and proliferative rate, breast tissue classified as normal or DH had a significantly higher percentage of type 1 lobules, while the SAD group had a significantly higher percentage of type 2 lobules. Furthermore, the number of proliferating cells was highest in the type 1 lobules for all tissues except BDA, in which the proliferative rate was highest in type 2 lobules. From these data, the following conclusions were drawn:

- Breast tissues obtained from biopsies performed because of mammographic or clinical abnormalities (even in the absence of cancer) have architectural and cell kinetic patterns that differ from those of tissues obtained at reduction mammoplasties. Even in cases where pathology was absent or was benign, the pattern of breast development was more similar to that of a cancer-bearing breast than it was to the population not requiring biopsy.

- In DH, type 1 lobules are the most frequent structures present, and they have the highest proliferative rate, supporting the postulate that this lesion arises from type 1 lobules. In contrast, type 2 and 3 lobules are more prominently represented and have a higher proliferative rate in more differentiated lesions, such as BDA and SAD.

Cancer risk — Several lines of evidence support the type 1 lobule as being the equivalent of the terminal ductal lobular unit [57,58] and the site of origin of ductal carcinomas (picture 15 and picture 16 and picture 17 and picture 18):

- In autopsy studies, the nontumoral parenchyma of breasts harboring a malignancy contains a significantly higher number of hyperplastic terminal ducts, atypical type 1 lobules, and ductal carcinoma in situ (DCIS) originating from type 1 lobule compared with those from breasts that are free of malignancy [40,51]. Thus, the type 1 lobule is affected by both preneoplastic and neoplastic processes.

- Although the breast tissue from parous women in the general population contains predominantly type 3 lobules and a very low percentage of type 1 lobules, the nontumoral breast tissue of parous women who have developed breast cancer (all of whom had a late first pregnancy or a family history of breast cancer in our studies) consists of predominantly type 1 lobules [51,59].

- The architectural pattern of nonmalignant breast tissue in parous women undergoing mastectomy for invasive breast cancer or prophylactic mastectomy because of a genetic predisposition to breast cancer differs from that of women undergoing

reduction mammoplasties, with a predominance of type 1 lobules, regardless of parity [13,50]. These observations suggest that genetic predisposition to breast cancer might affect genes that control the branching pattern of the breast during lobular development.

- The type 1 lobules are most numerous in the breasts of nulliparous women, who are at a higher risk of breast cancer than parous women [13]. (See 'Menopause' above.)

More differentiated lobular structures, such as type 2 lobules, are affected by other types of neoplastic lesions, notably lobular carcinomas (picture 19) [40].

Defective regulation of epithelial growth — The molecular mechanisms underlying the development of breast cancer, particularly estrogen-associated carcinogenesis, are incompletely understood. It is generally believed that the initiation of breast cancer results from uncontrolled cellular proliferation and/or aberrant apoptosis as a consequence of cumulative genetic damages that activate proto-oncogenes and/or inactivate tumor suppressor genes. These genetic alterations can be inherited as germline mutations or be acquired (somatic mutations) as a result of cumulative exposure to environmental carcinogens (see "Overview of hereditary breast and ovarian cancer syndromes"). The classic two-stage model of carcinogenesis further postulates that the altered genotype of the initiated cell is irreversible and that tumor progression, the second stage in carcinogenesis, depends upon further epigenetic changes that are potentially reversible.

It remains to be determined whether this animal model of chemical carcinogenesis holds true for breast cancer and what role is played by estrogen. In rodent models of carcinogen-induced and spontaneous mammary cancer, prolonged exposure to both estrogens and progestins can support initial tumor formation and early tumor growth. In vitro, 17-beta estradiol induces phenotypic changes indicative of neoplastic transformation in cultured human breast epithelial cells that are similar to those induced by the chemical carcinogen benzo[a]pyrene [60]. Furthermore, human studies now provide a clear link between exposure to exogenous hormones and a risk for breast cancer. (See "Menopausal hormone therapy: Benefits and risks".)

Although some breast cancers may be related to cumulative hormonal exposures, others, particularly those with an inherited genetic susceptibility, may be caused by an unusual sensitivity to pubertal hormones. As an example, in a case-control study of disease-concordant monozygotic twins, the twin with earlier onset of menses was five times more likely to be diagnosed with breast cancer before the other [61]. In contrast, other hormonal factors (ie, later first pregnancy, lower parity, later menopause) did not predict an earlier diagnosis when both twins were affected. These data suggest that genotypic differences exist, even among patients with an inherited genetic susceptibility.

Even though the cause of breast cancer and the ultimate mechanisms through which an early pregnancy protects from cancer development remain largely unknown, comparative studies of normal and neoplastic breast development have unraveled similarities with experimental models that validate their extrapolation for testing hypotheses on the initiation and progression of human breast cancer. From these studies, the following can be concluded:

- The process of mammary gland differentiation is the result of complex interactions of ovarian, pituitary, and placental hormones, which in turn induce inhibition of cell proliferation, downregulation of estrogen receptors and progesterone receptors, activation of specific genes, and expression of extracellular matrix proteins in the normal breast. Findings in experimental animal models indicate that induction of mammary cancer with chemical carcinogens is only successful when the carcinogen interacts with an undifferentiated and highly proliferating mammary epithelium, whereas differentiation of the mammary gland inhibits carcinogenic initiation [35,62]. These data support the view that breast cancer arises in women whose breasts have failed to achieve an optimal degree of differentiation.

- Cellular susceptibility to transformation by estrogens may depend more on proliferative rate and genetic predisposition than hormone receptor content, similar to what has been observed with chemical carcinogenesis [43,63,64]. The independence of estrogen receptor content and estrogen-induced carcinogenesis would support the postulate that metabolic activation of estrogen is involved in the neoplastic transformation of susceptible breast epithelial cells. Alternatively, estrogen and/or its metabolites may act instead to promote neoplastic progression in chemically transformed breast epithelial cells.

- In experimental animals, the protective effect exerted by pregnancy on mammary carcinogenesis can be mimicked by treatment with the placental hormone chorionic gonadotropin. These data open the possibility of preventing breast cancer by treating young, nulliparous females with hormones that mimic a full-term pregnancy, inducing complete differentiation of the gland [65,66].

- Particularly in view of the fact that the terminal ductal lobular units are thought to represent the site of origin of mammary carcinomas, partial or incomplete menopausal breast involution (or reactivation of type 1 lobules under the influence of postmenopausal hormone therapy) may also interact with other risk factors such as parity, age at first birth, the presence of benign breast disease, and family history to influence the risk of breast cancer [50,52]. (See 'Parity, lobular differentiation, and breast cancer risk' above.)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Normal puberty (The Basics)" and "Patient education: Early puberty (The Basics)" and "Patient education: Late puberty (The Basics)")

SUMMARY

- **Anatomy –** The breast comprises three major structures: skin, subcutaneous tissue, and breast tissue. (See 'Anatomy' above.)
    - **Histology –** Breast tissue is composed of both epithelial and stromal elements. The epithelial components are branching ducts that connect the structural and functional units of the breast (the lobules) to the nipple. The stroma, which comprises the majority of the breast volume in the nonlactating state, is composed of adipose and fibrous connective tissue. (See 'Histology' above.)
    - **Blood supply –** The principal blood supply of the breast is derived from the internal mammary artery. Approximately one-third of the blood supply (mainly to the upper outer quadrant) is provided by the lateral thoracic arteries. (See 'Blood supply and lymphatic drainage' above.)
    - **Lymphatic drainage –** Lymph flow from the deep subcutaneous and intramammary vessels moves centrifugally toward the axillary and internal mammary lymph nodes. The majority (97 percent) of the lymph flows to the axillary nodes. (See 'Blood supply and lymphatic drainage' above.)

- **Normal development** – Human breast development is a progressive process that is initiated during embryonic life. Although puberty marks the beginning of glandular maturation, full breast differentiation is attained only with subsequent pregnancy and lactation. (See 'Normal development' above.)

    - **Pregnancy and lactation** – During pregnancy, the maximum branching capability of the breast is expressed, and the secretory acinus that is formed during pregnancy represents a terminal outgrowth that marks the full extent of glandular differentiation. Fully differentiated secretory cells are characterized by their ability to synthesize and secrete milk proteins and lipids. (See 'Pregnancy and lactation' above.)

    - **Involution** – The postlactational breast requires a combination of lactogenic hormone deprivation and local signals to undergo glandular regression (involution), a process characterized by apoptotic cell death and tissue remodeling. (See 'Lobular involution (regression)' above.)

    - **Menopause** – After menopause, the breast undergoes regression, with atrophy of the glandular elements and a marked decrease in the number of lobules. Concurrently, the fibrous connective tissue component of the stroma decreases, and adipose tissue accumulates. (See 'Menopause' above.)

- **Hormonal influences** – Normal ductal development requires both estrogen and progesterone. Progesterone acts in conjunction with estrogen to regulate breast development through its specific receptor on breast epithelial cells. (See 'Hormonal influences on breast development' above.)

- **Parity, lobular differentiation, and breast cancer risk** – Parity influences the lobular composition as well as the proliferative activity of the breast. The lobules of nulliparous women have a higher proliferative activity than those of parous women. These differences may influence the risk of developing breast cancer. (See 'Parity, lobular differentiation, and breast cancer risk' above.)

- **Architectural patterns and breast pathology** – Breast disease may develop in response to variations in development, proliferative activity, and hormone receptor content in the mature breast. (See 'Architectural patterns and breast pathology' above.)

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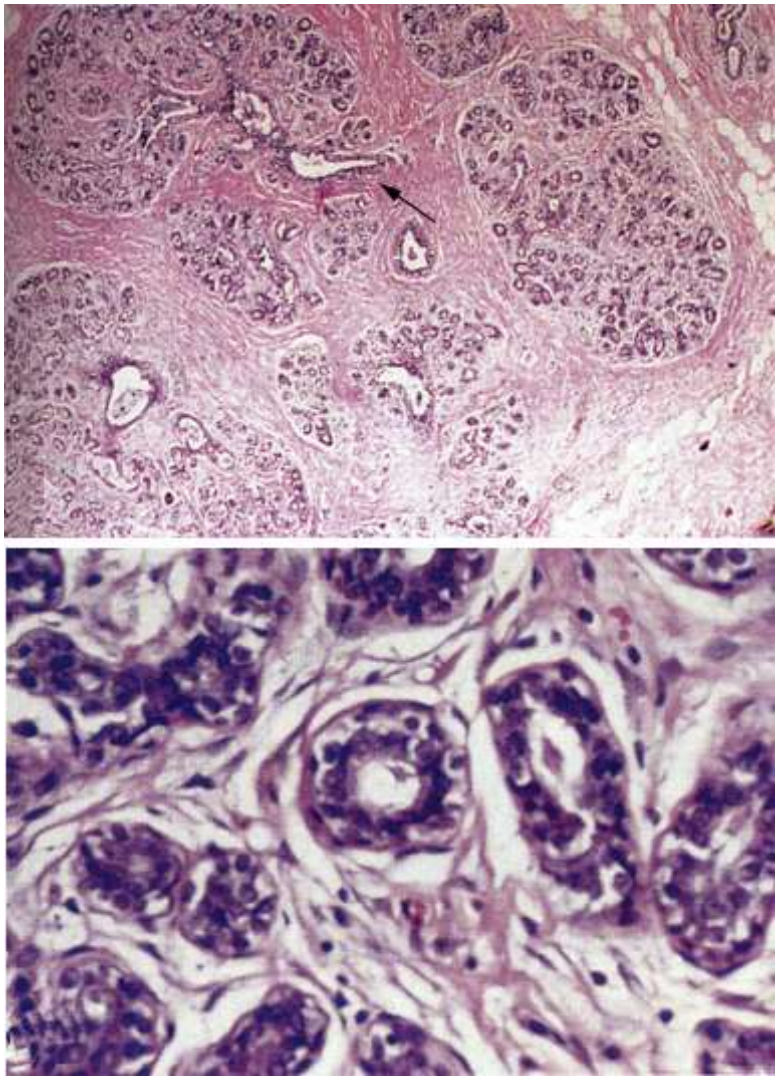
Topic 812 Version 32.0

GRAPHICS

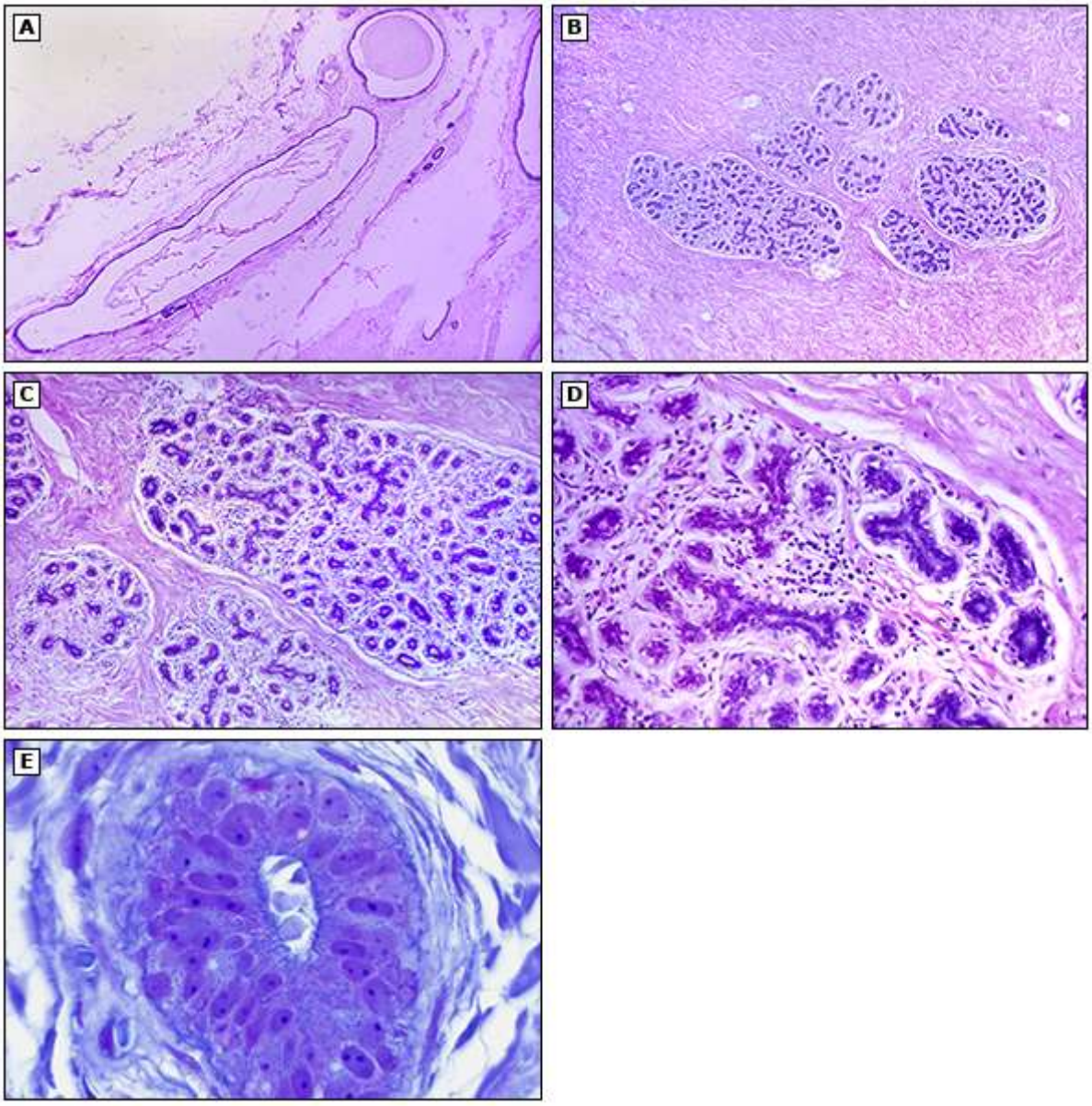
Histology of normal breast tissue of a premenopausal woman



Upper panel, low power photomicrograph, showing several lobules and a few extralobular ducts (arrow); lower panel, high power photomicrograph of several acini of a lobule.

Graphic 68667 Version 1.0

Breast - Normal terminal ductal lobular units



Histology of normal female breast ducts and terminal ductal lobular units (TDLU):

(A) Major duct at low magnification (6.3x) (slide 11).

(B) Several TDLU at low magnification (10x) (slide 16).

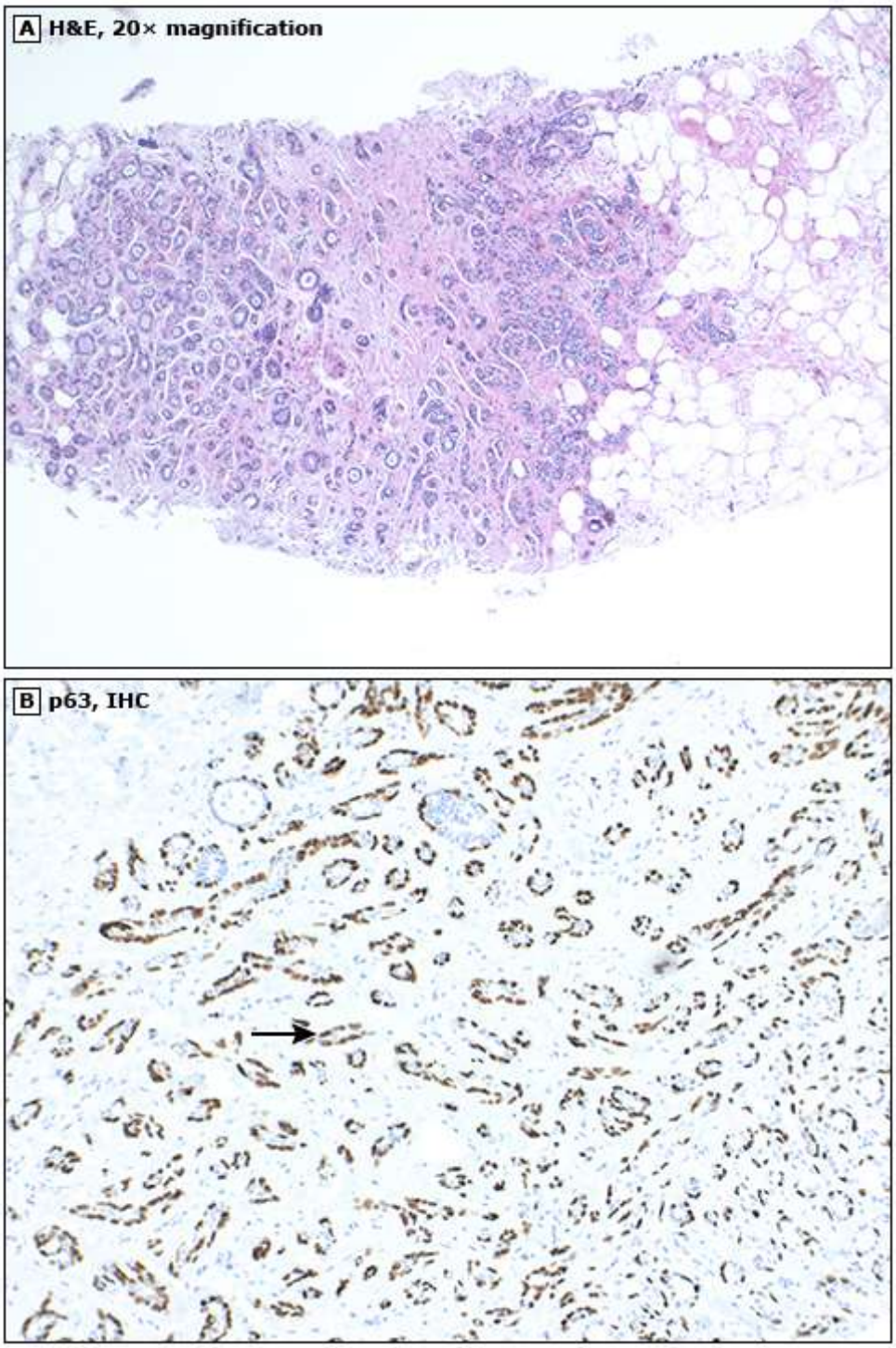
(C) Sharp interphase between dense extralobular connective tissue and each TDLU (25x magnification) (slide 17).

(D) Loose intralobular stroma investing ductules (63x magnification) (slide 18).

(E) Single duct cut transversely revealing an inner layer of secretory cells with abundant mitochndria and an outer sparse cell layer of myoepithelium with sparse cytoplasm (25x magnification).

Graphic 91348 Version 2.0

Immunohistochemical (IHC) stain p63 demonstrates myoepithelial cells around benign glands in sclerosing adenosis

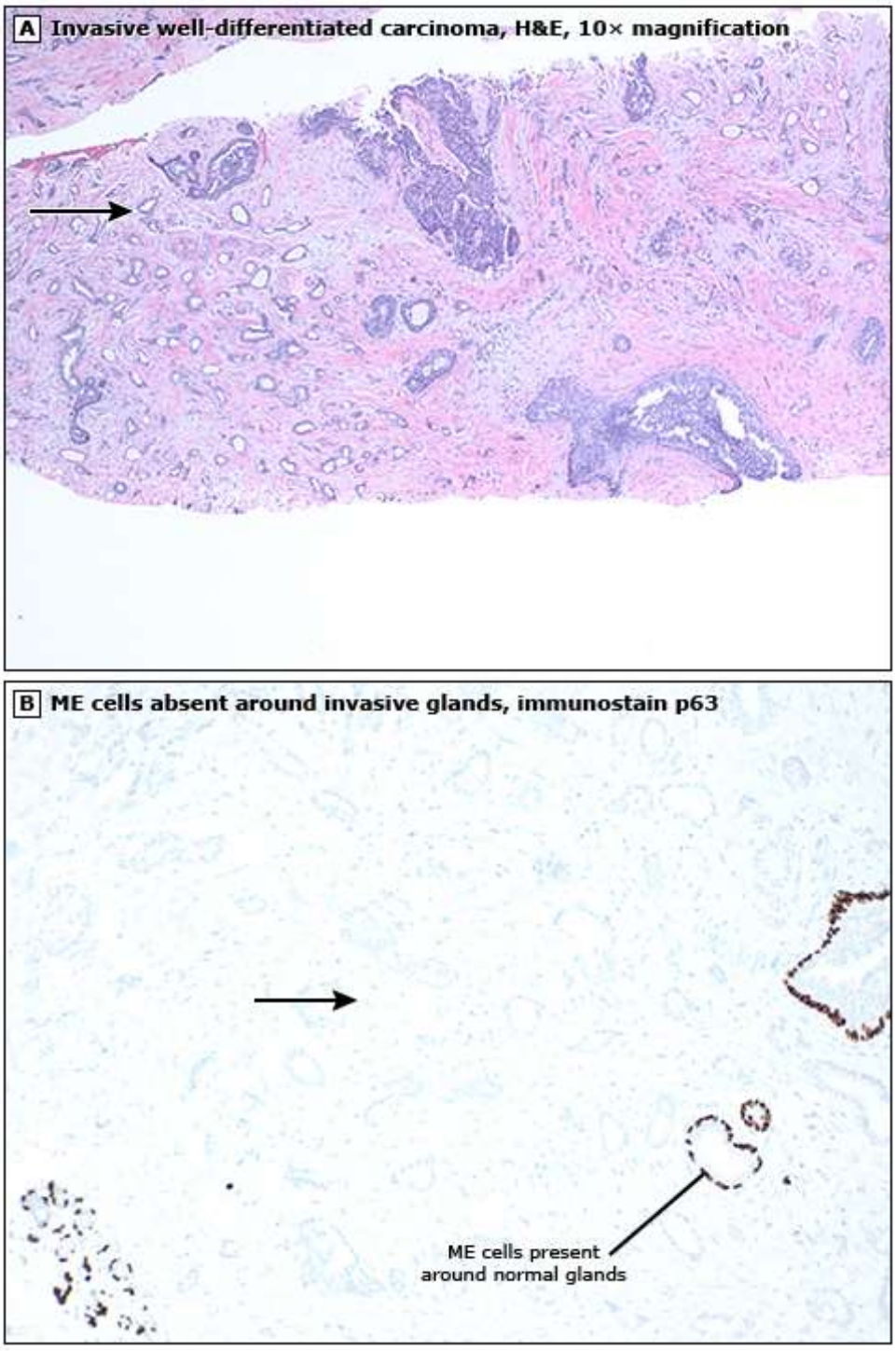


In sclerosing adenosis and nipple adenomas, which are benign lesions, the two-cell layer is evident by routine histologic examination or ancillary IHC stains to detect the presence of the myoepithelial cell layer.

H&E: hematoxylin and eosin stain.

Graphic 138842 Version 1.0

H&E of invasive ductal carcinoma and immunohistochemical (IHC) stain p63 shows absence of ME cells around invasive glands

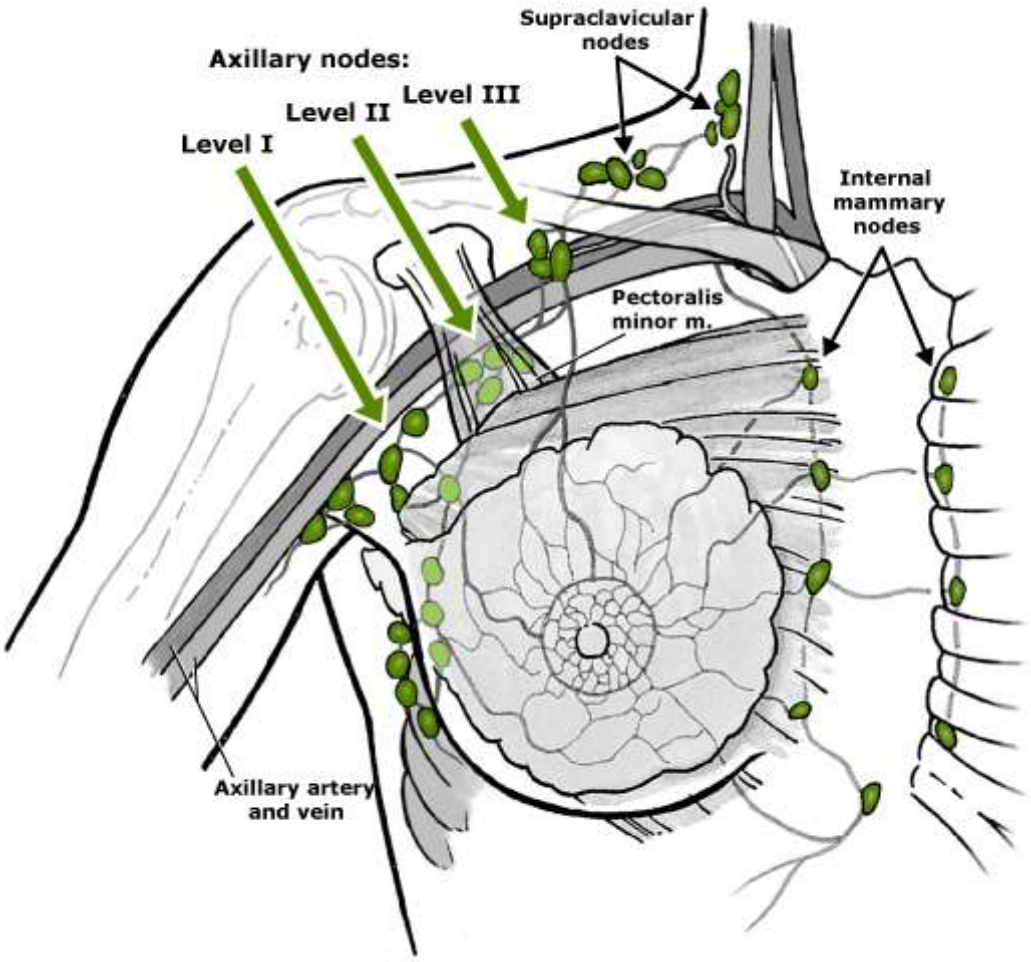


In well-differentiated malignancies like tubular carcinoma, the myoepithelial cell layer is lost around invasive glands and confirms the malignant nature of these lesions.

H&E: hematoxylin and eosin stain; ME: myoepithelial.

Graphic 138841 Version 1.0

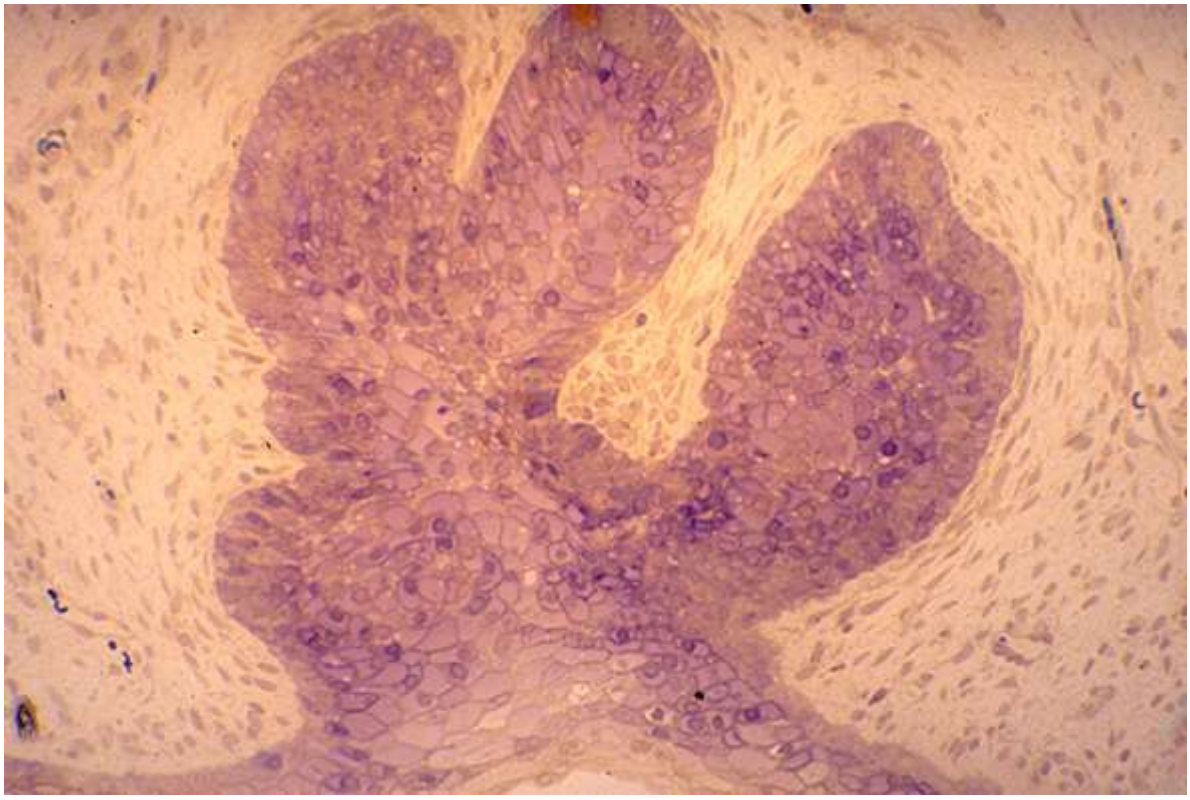
Lymphatic drainage of the breast



The lymphatic drainage of the breast flows toward the axillary and internal mammary lymph nodes.

Graphic 74746 Version 4.0

Fetal milk line development

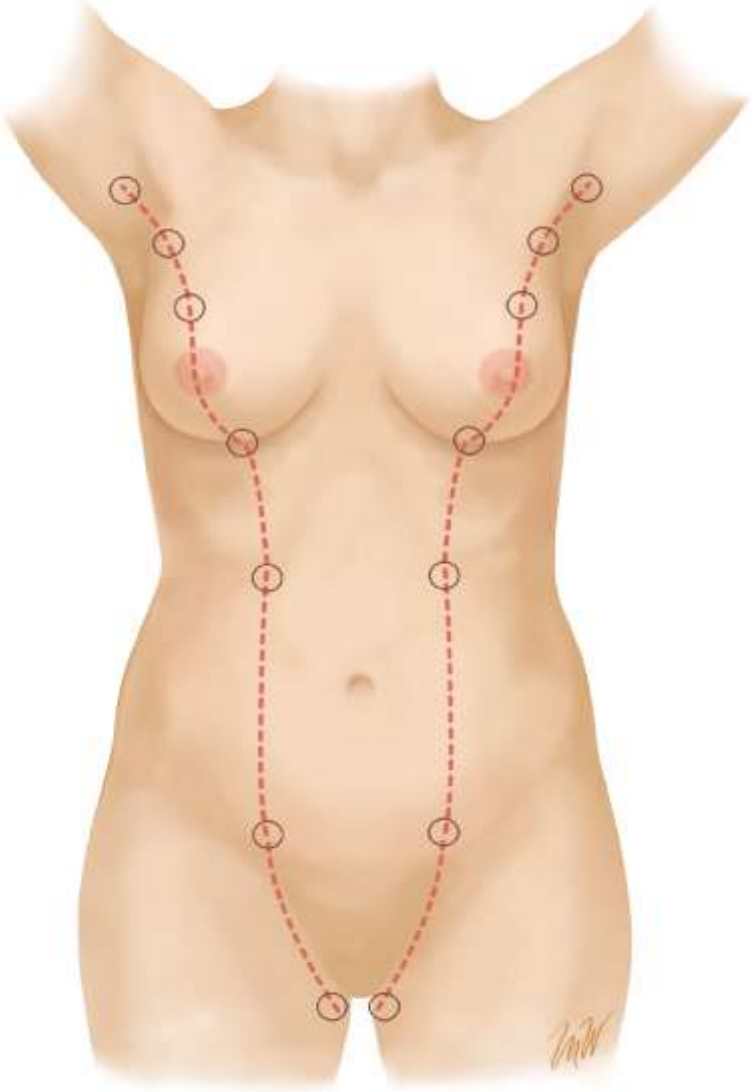


The milk line develops in utero as an epidermal-derived structure from the skin.

Reproduced with permission from: The Anatomy and Histology of the Normal Human Breast. Images and text by Dr. Hanne Jensen.

Graphic 91347 Version 3.0

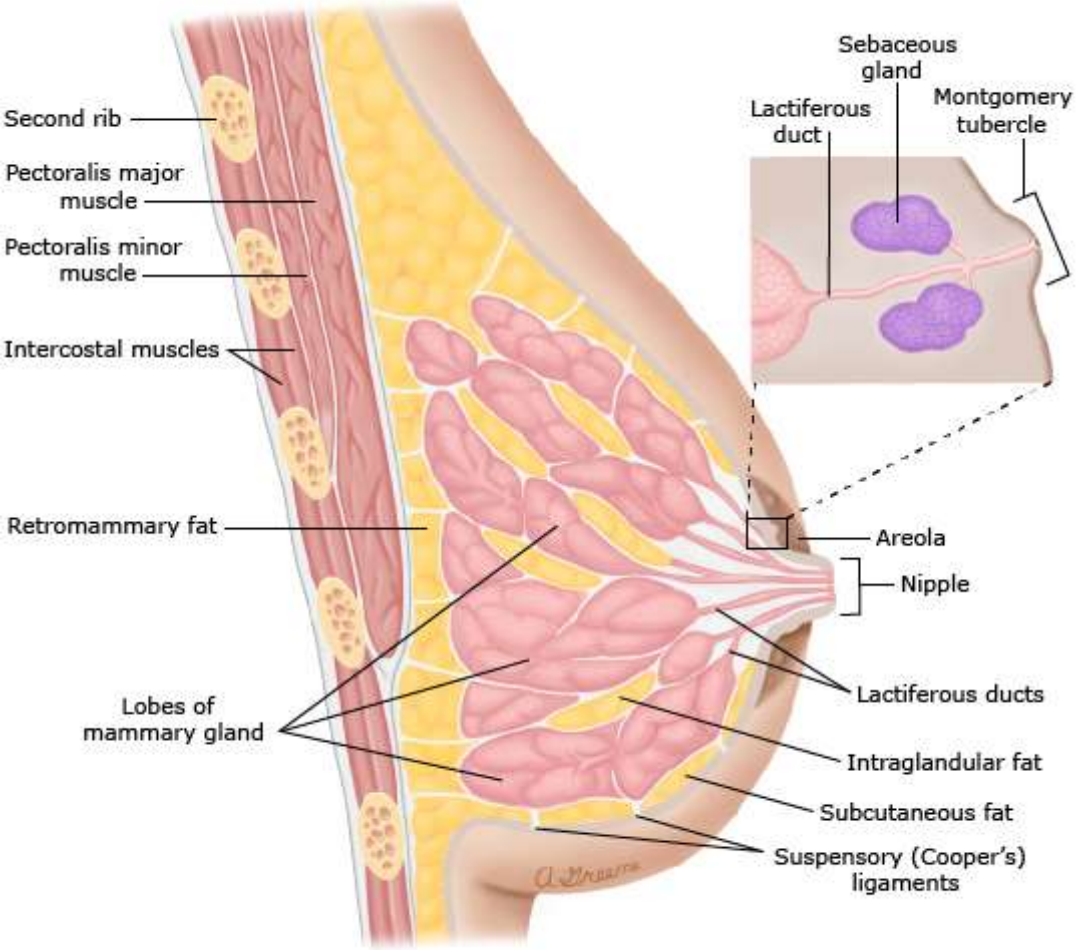
Breast development and milk lines



Polymastia (supernumerary breasts) and polythelia (supernumerary nipples) may develop in males and females anywhere along the length of the mammary ridges (milk lines). Breast tissue may not develop (amastia), or there may be nipple development but no breast tissue (amazia).

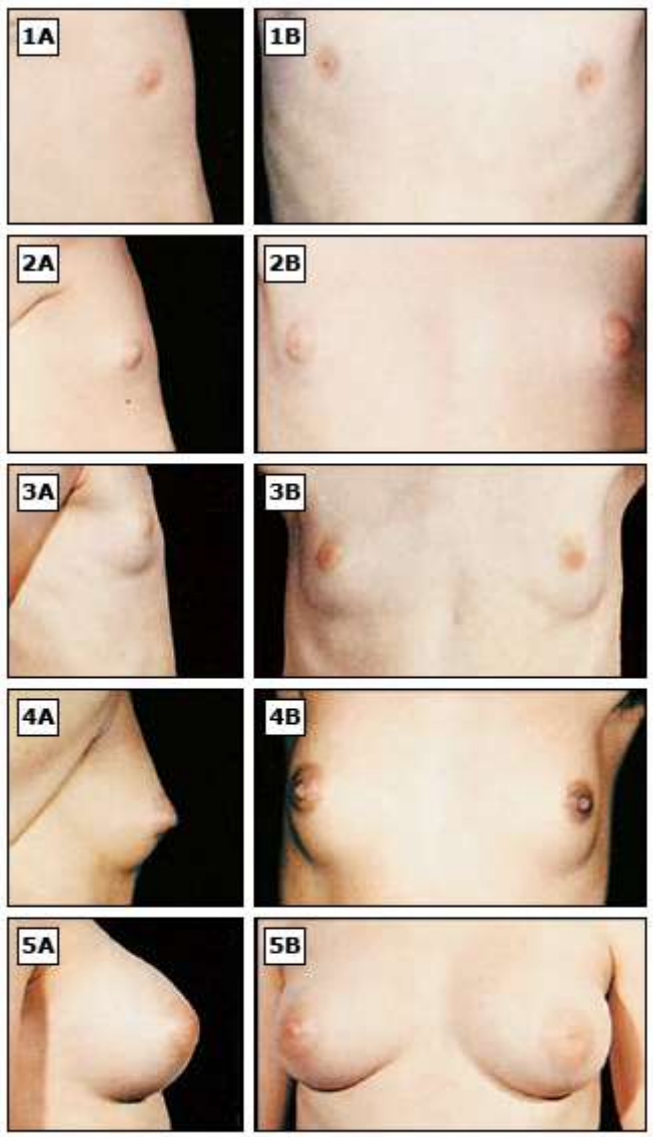
Graphic 63944 Version 2.0

Anatomy of the breast



Graphic 88523 Version 4.0

Sexual maturity rating (Tanner staging) of breast development in females



Stages in breast development in females.

Stage 1 – Prepubertal, with no palpable breast tissue.

Stage 2 – Development of a breast bud, with elevation of the papilla and enlargement of the areolar diameter.

Stage 3 – Enlargement of the breast, without separation of areolar contour from the breast.

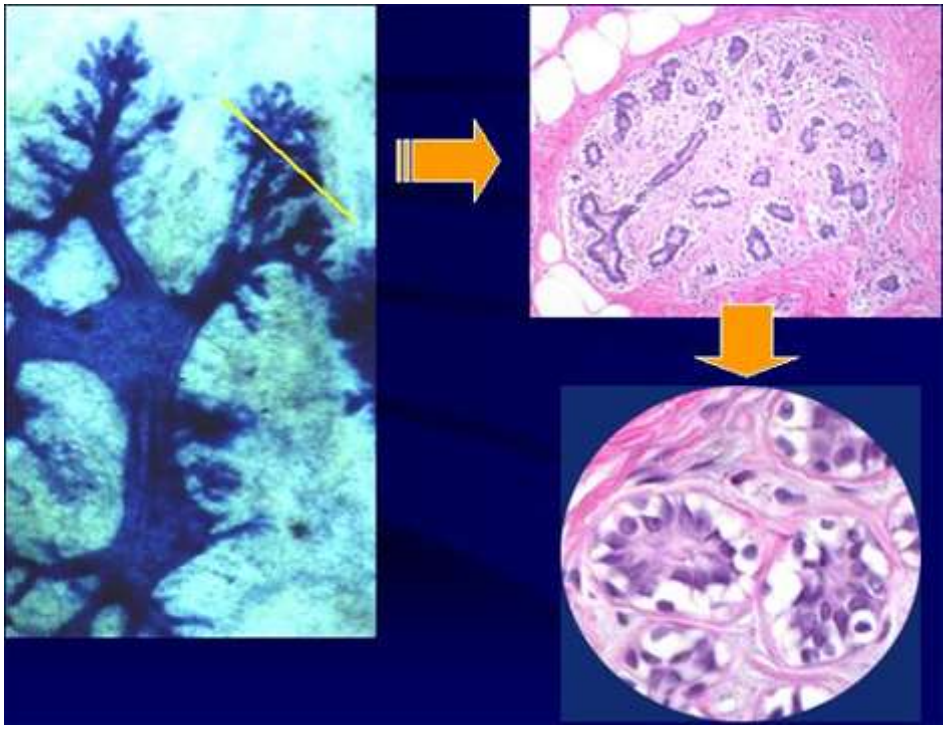
Stage 4 – The areola and papilla project above the breast, forming a secondary mound.

Stage 5 – Recession of the areola to match the contour of the breast; the papilla projects beyond the contour of the areola and breast.

Figure from: Roede MJ, van Wieringen JC. Growth diagrams 1980: Netherlands third nation-wide survey. Tijdschr Soc Gezondheids 1985; 63:1. Reproduced with permission from the author.

Graphic 72038 Version 11.0

Type 1 breast lobule



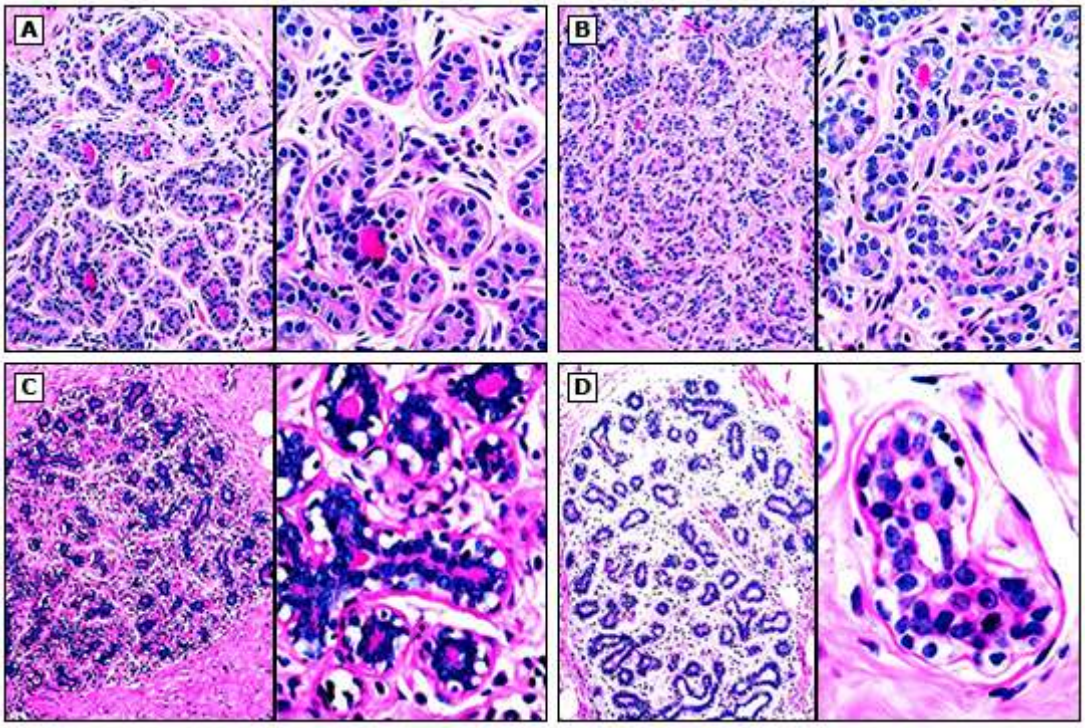
Whole mount preparation of breast tissue of an 18-year-old nulliparous woman showing histology of type 1 breast lobules as viewed by light microscopy.

(Left panel) Tissue section stained with toluidine blue. 2.5×.

(Right panels) Histologic section of lobule type 1 stained with hematoxylin and eosin (H&E). Photographs at 10× and 40×, respectively.

Graphic 52636 Version 7.0

Breast morphological changes with the menstrual cycle



Changes in normal breast morphology with normal menstrual cycle stages (left panel low magnification, right panel high magnification):

(A) Stage 1 of menstrual cycle. Low magnification of lobule showing acini clustered with barely perceptible epithelial and myoepithelial layer. Nuclei are round to oval with basophilic cytoplasm and sparse stromal infiltrate, with occasional sprinkling of mast cells seen. Eosinophilic secretions are noted within the lumina. Higher magnification of lobule showing the uniform lack of vacuolation.

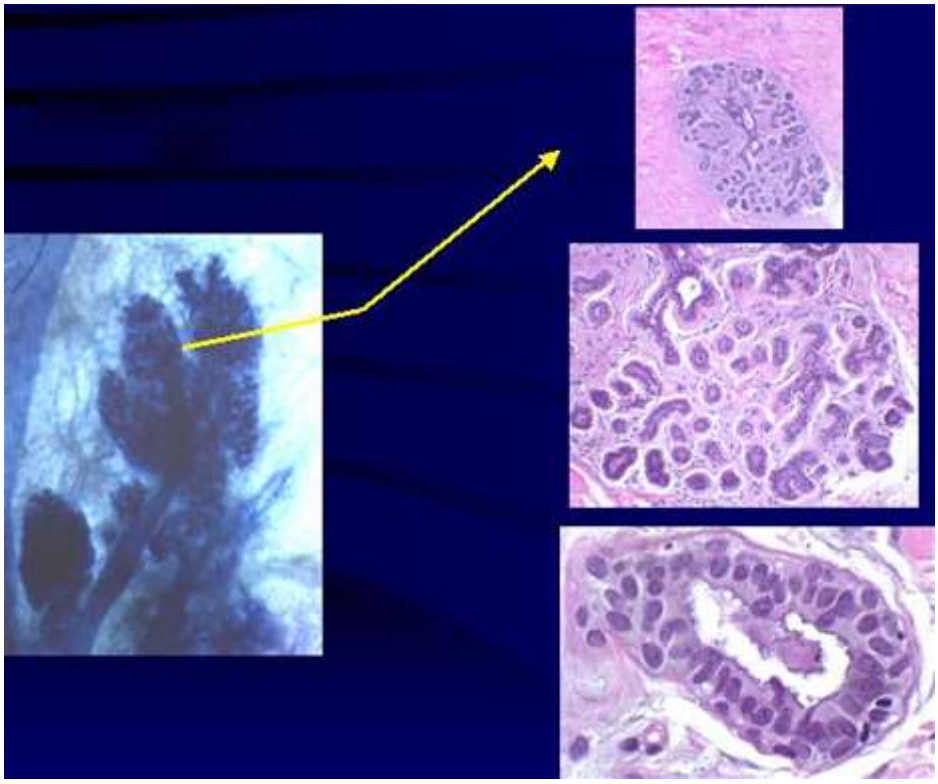
(B) Stage 2 of menstrual cycle. Low magnification of lobule showing appearance of vacuolation in the myoepithelial layer with prominent distinction between the two layers of the acini. High magnification of lobule showing increasing tendency for basal vacuolation.

(C) Stage 3 of menstrual cycle. Low magnification of lobule showing prominent myoepithelial vacuolation with edema of the stroma. The eosinophilic secretions within the lumina are present. High magnification of the acini showing prominent vacuolation.

(D) Stage 4 of menstrual cycle. Low magnification of lobule showing extensive stromal edema and infiltrate with myoepithelial vacuolization. High magnification of the acini showing prominent mitotic figure and apoptotic body in the epithelial layer.

Graphic 91351 Version 3.0

Type 2 breast lobule



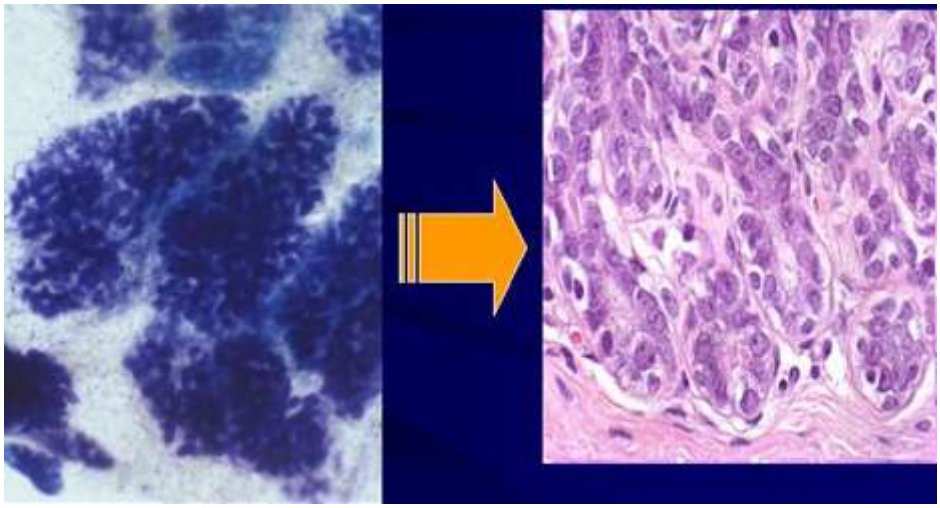
Whole mount preparation of breast tissue of a 24-year-old nulliparous woman showing type 2 breast lobules as viewed by light microscopy.

(Left panel) Tissue section stained with toluidine blue. 2.5×.

(Right panels) Histologic section of lobule type 2 stained with hematoxylin and eosin (H&E). Photographs at 10× and 40×, respectively.

Graphic 64382 Version 6.0

Type 3 breast lobule



Whole mount preparation of breast tissue of a 35-year-old parous woman showing type 3 breast lobule as viewed by light microscopy.

(Left panel) Tissue section stained with toluidine blue × 2.5. (Right panel) Histologic section of lobule type 3 stained with hematoxylin and eosin (H&E). Photographs at 10× (left panel) and 40× (right panel), respectively.

Graphic 72142 Version 5.0

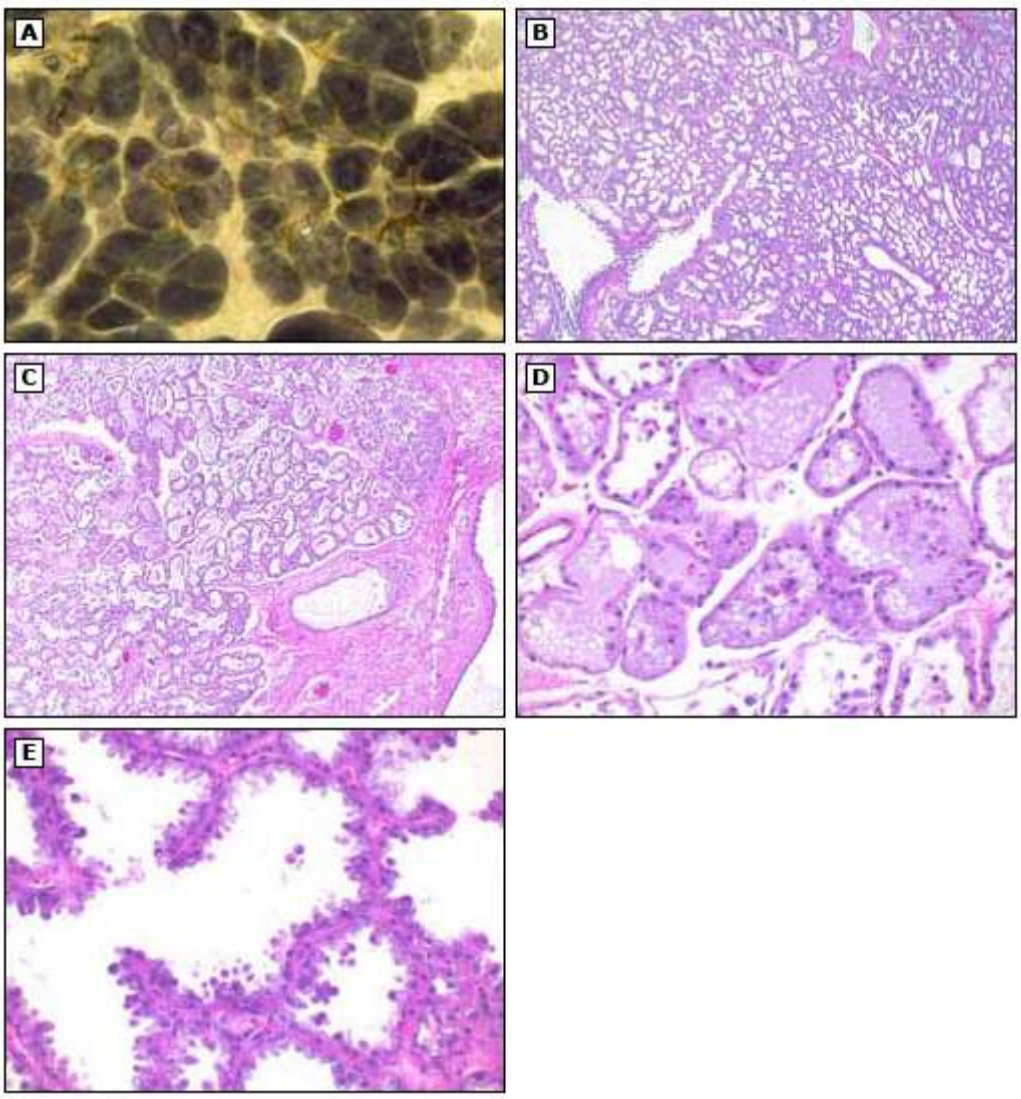
Characteristics of human breast lobules

Lobule type	Lobule area (mm^2)	No. of components per lobule	No. of cells/cross section
Type 1	0.048±0.044	11.2±6.3	32.4±14.1
Type 2	0.060±0.026	47.0±11.7	13.1±4.8
Type 3	0.129±0.049	81.0±16.6	11.0±2.0

Data from: Russo J, et al, Breast Cancer Res and Treat 1992; 23:211-218 and Russo J, Russo IH. Development of human mammary gland. In: Neville MC, Daniel CW, eds. The mammary gland. New York, Plenum, 1987; p 67.

Graphic 74484 Version 5.0

Breast morphological changes with pregnancy and lactation



The breast terminal ductal and lobular units (TDLUs) undergo marked physiologic changes during pregnancy and lactation as shown in the following images:

(A) Pregnancy hormones induce hyperplasia of TDLUs. This image depicts the changes in a woman who is five months pregnant. Note the enlarged lobules have crowded out the extralobular connective tissue.

(B) Low-magnification image of a lactating mammary gland of a young woman. Note that the alveoli fill the entire mammary gland without evidence of residual fat cells.

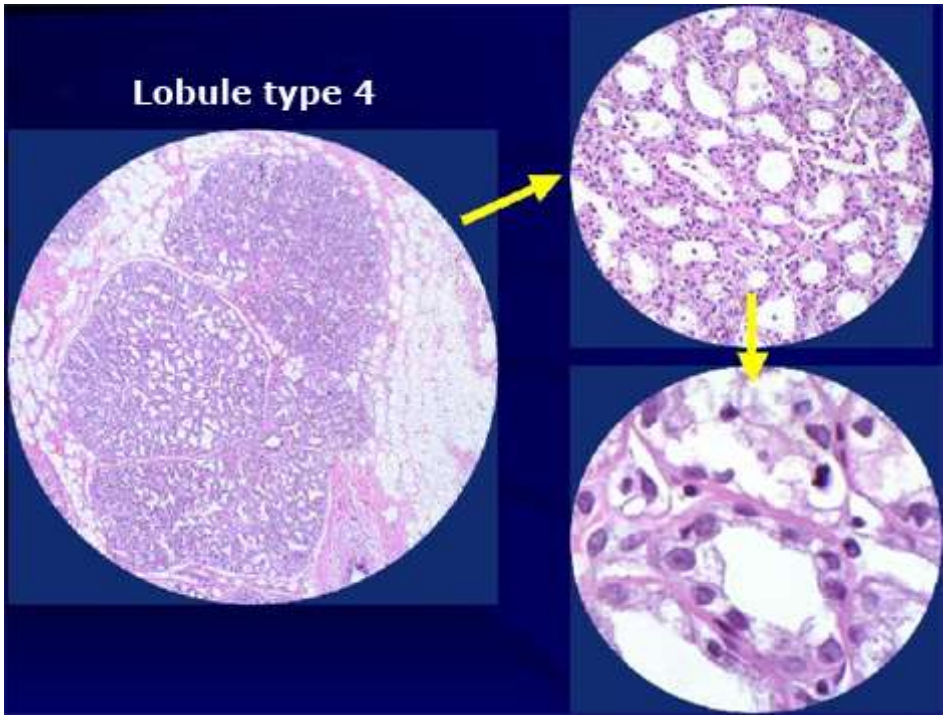
(C) TDLUs of the lactating mammary gland of a young woman. Medium magnification.

(D) Lactating mammary gland of a young woman. Note that the lumens are filled with a proteinaceous fluid with clear lipid vacuoles. The epithelium is attenuated.

(E) Lactating mammary gland of a young woman showing lumens filled with fluid. The tall columnar cells have clear lipid vacuoles.

Graphic 91352 Version 4.0

Type 4 breast lobule



This is a type 4 breast lobule obtained at the beginning of lactation as viewed by light microscopy.

Microscopic sections fixed and stained with hematoxylin and eosin (H&E). Photographs at 2.5× and 40×, respectively.

Graphic 51142 Version 4.0

Breast lobules - Normal atrophy with time

The normal breast lobules atrophy with the age of the woman.

(A) Normal breast lobule in premenopausal woman age 43 years. Note thickened basement membrane around ductules and early sclerotic changes of the lobule. (63x magnification).

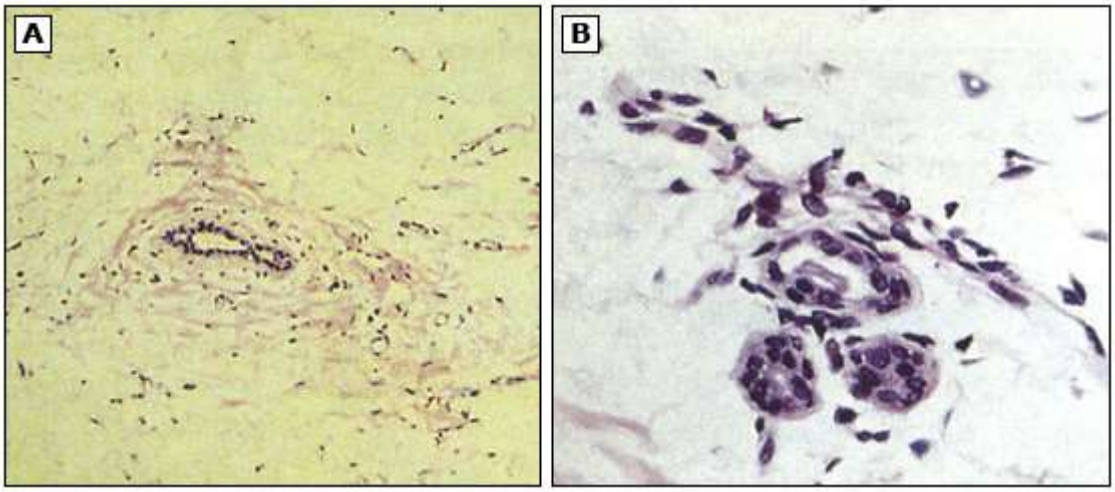
(B) Normal breast in postmenopausal woman showing moderate atrophy of the lobules. (8x magnification).

(C) Normal breast in postmenopausal woman showing complete atrophy of the terminal ductal lobular unit. (1x magnification).

(D) Higher power magnification of normal breast in postmenopausal woman showing complete atrophy of the terminal ductal lobular unit. (4x magnification).

Graphic 91349 Version 2.0

Atrophy of breast tissue in menopause



A section of breast tissue from a postmenopausal woman demonstrating atrophy of the glandular tissues. The stroma is composed primarily of adipose tissue.

(A) Lower-power view of an atrophic lobule.

(B) Higher-power view of an atrophic lobule.

Graphic 77903 Version 2.0

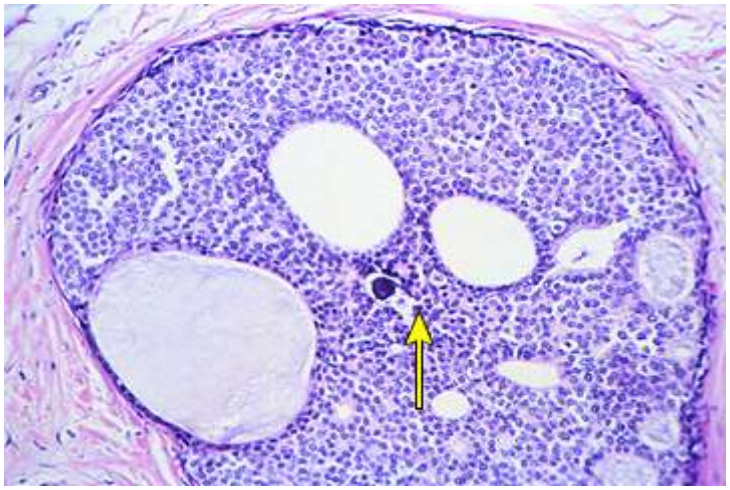
Distribution of Ki67, ER-α, and PgR-positive cells in the lobular structures of the human breast

Lobule type	No. cells	Percentage of positive cells (mean ± standard deviation)				
		Ki67	ER	PgR	Ki67 + ER	Ki67 + PgR
Lobule 1	19,339	4.72±1.00	7.46±2.88	5.70±1.36	0.48±0.28	0.09±0.01
Lobule 2	8490	1.58±0.45	3.83±2.44	0.73±0.57	0.31±0.21	0.28±0.27
Lobule 3	17,750	0.40±0.18	0.76±0.04	0.09±0.04	0.01±0.01	0.01±0.01

Russo J, et al. Breast Cancer Res Treatment 1999; 53:217. Reprinted with permission by Kluwer Academic Publishers.

Graphic 61091 Version 4.0

Cribriform ductal carcinoma in situ

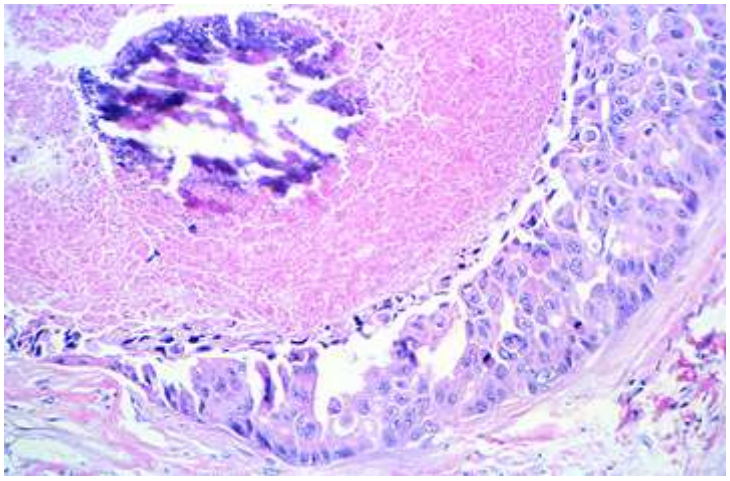


Light micrograph of a lesion from the breast of a woman with cribriform ductal carcinoma in situ shows a back to back glandular growth pattern. The nuclei are well differentiated (low grade). A small calcification is noted near the center of the involved space (arrow).

Courtesy of Stuart Schnitt, MD.

Graphic 71553 Version 3.0

Comedo ductal carcinoma in situ



Light microscopic specimen of comedo ductal carcinoma in situ shows a large central area of necrosis that is focally calcified. The nuclei are poorly differentiated (high grade).

Courtesy of Stuart Schnitt, MD.

Graphic 77048 Version 2.0

Grade I infiltrating ductal carcinoma of the breast

(Panel A) Low-power view of a well-differentiated infiltrating ductal carcinoma shows tumor cells that infiltrate the stroma as solid nests and glands.

(Panel B) High-power view demonstrates relatively uniform nuclei with no evidence of mitotic activity.

Courtesy of Stuart Schnitt, MD.

Graphic 76328 Version 5.0

Grade III infiltrating ductal carcinoma of the breast

(Panel A) Low-power view of a poorly differentiated breast carcinoma shows that the tumor is composed of solid nests of neoplastic cells without evidence of gland formation.

(Panel B) The high-power view demonstrates marked nuclear atypia in the tumor cells with considerable mitotic activity.

Courtesy of Stuart Schnitt, MD.

Graphic 67082 Version 5.0

Infiltrating lobular carcinoma of the breast

(Panel A) Low-power view of an infiltrating lobular breast carcinoma shows small tumor cells that infiltrate the stroma singly and in a single-file pattern.

(Panel B) High-power view demonstrates that the tumor cells are relatively small and uniform in appearance.

Courtesy of Stuart Schnitt, MD.

Graphic 54150 Version 4.0

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Malini Harigopal, MD No relevant financial relationship(s) with ineligible companies to disclose. **Kamaljeet Singh, MD** No relevant financial relationship(s) with ineligible companies to disclose. **Anees B Chagpar, MD, MSc, MA, MPH, MBA, FACS, FRCS(C)** Consultant/Advisory Boards: Guardant Health [Breast cancer]; Merck [Breast cancer]; Novartis [Breast cancer]; Protean BioDiagnostics [Breast cancer]; Sanofi-Aventis [Breast cancer]. Speaker's Bureau: Merck [Breast cancer]. All of the relevant financial relationships listed have been mitigated. **Wenliang Chen, MD, PhD** No relevant financial relationship(s) with ineligible companies to disclose.

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