Breast development and morphology

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NEWER VERSION OF TOPIC MESSAGE

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 them, is pertinent to the study of both premalignant and malignant conditions affecting the breast.

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 which connect the structural and functional units of the breast (the lobules) to the nipple (picture 1). The stroma, which comprises the majority of the breast volume in the non-lactating state, is composed of adipose...
and fibrous connective tissue (picture 2).
The skin of the breast is thin, and contains hair follicles, sebaceous glands, and exocrine sweat glands. The nipple has abundant sensory nerve endings and sebaceous and apocrine sweat glands, but not hair follicles. The areola is more or less circular and pigmented, measuring 15 to 60 mm in diameter. The Morgagni tubercles, which are located near the periphery of the areola, are elevations formed by the openings of the ducts of the Montgomery glands, large sebaceous glands that represent an intermediate stage between sweat and mammary glands. 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.

**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 [6]. 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 [6]. 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 [7].

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 [8]. 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) [8]. 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. (See "Management of the regional lymph nodes in breast cancer", section on 'Extent of dissection'.)

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

At birth, the breast rudiment is formed by 10 to 12 primitive ductal elements located beneath the nipple-areola 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.

**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 2 and figure 2) [3]. The external appearance of the breast from childhood to maturity has been divided into five phases by Tanner (picture 4). (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 (virginal) lobule (picture 5). 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 6); 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 7 and picture 8). 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 type 3 lobule, respectively (table 1). This increases the size of the lobules, and reduces the size of each individual alveolar bud. The alveolar buds composing a type 1 lobule are practically twice the size of those of type 2 lobules, whereas the reduction in size in ductules (or alveoli) of type 3 lobules is less dramatic, although still significant (table 1).

Parity and age both influence breast architecture [3,10]. 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. All of these structures are found in an almost constant proportion through the woman's life span, and are not influenced by age or menopausal status. 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). In such women, the frequency of type 3 lobules peaks during the early reproductive years, and starts to decrease in the 30s, probably due to their involution (regression) to predominantly type 1 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).

**Pregnancy and lactation** — The pregnant woman undergoes anatomic and physiologic changes in almost every organ system. (See "Maternal endocrine and metabolic adaptation to pregnancy".) 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 9). (See "Physiology of lactation".)

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 type 3 lobule to a type 4 lobule (picture 10). In these newly formed lobules, the epithelial cells composing each acinus not only increase greatly in number due to active cell division but they 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 histological 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 [11,12].

**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 11). 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 12).
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 [3,10].

ABNORMALITIES IN BREAST DEVELOPMENT

Congenital — The most common congenital abnormality of breast development, which can be seen both in boys and girls, is an accessory or supernumerary nipple (polythelia). Ectopic nipple tissue may occur at any point along the milk streak from the axilla to the groin. Rarely, accessory true mammary glands develop, most commonly in the axilla (polymastia). 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 [13]. 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 [14-18]. Rare anomalies of the breast include [19,20]:

- Hypoplasia – underdevelopment of the breast
- Amastia – congenital absence of the breast
- Amazia – absence of breast tissue but a normal nipple-areola 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 [19]. These anomalies are amenable to reconstructive procedures [20-23]. 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 [24]. 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) [21,25-27]. These anomalies may result from diminished blood flow in the subclavian artery during early fetal development. (See "Diseases of the chest wall".)

Premature thelarche — Early breast development in girls (premature thelarche) is discussed separately. (See "Definition, etiology, and
evaluation of precocious puberty”.

**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 a nonobese woman [28]. A mammoplasty can be performed to achieve symmetry with the contralateral breast.

**HORMONAL INFLUENCES ON BREAST DEVELOPMENT** — Normal mammary growth, differentiation, and regression is 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 [29,30].

**Estrogens and progesterone** — 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 [29]. These biologic activities are thought to be predominantly mediated by a nuclear estrogen receptor (ER alpha), which activates transcription of specific genes containing the estrogen response elements [31]. 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 [32]. 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 "Physiology of the 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 [10,29,30,33]. 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 to 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 3-
fold in the type 2 lobules, and 10-fold in the type 3 lobules (table 2) [30,34]. The content of ER-alpha and PR in the lobular structures of the breast is directly proportional to the rate of cellular proliferation [34]. Type 1 lobules consistently contain a higher percentage of ER and PR-positive cells than do type 2 or 3 lobules, indicating a progressive decrease 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 [2,35-41], 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 [34].

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 [10]. 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 11). Another important difference is the higher proliferative activity in the type 1 lobules of nulliparous as compared to 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 [10]. 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 [42-44]. 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 [44-46]. Support for these observations was provided in a report that focused on breast biopsy specimens from 8736 women with benign breast disease [47]. 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 to 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 none, 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 a weak or no family history of breast cancer who had complete involution had a risk for breast cancer that was five-fold 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 [48,49]. 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 [48]. 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 step-wise 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 [48].

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 [45]. This data also raises 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 [50].

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 are reviewed elsewhere. (See "Overview of benign breast disease" and "Breast cysts: Clinical manifestations, diagnosis, and management" and "Atypia and lobular carcinoma in situ: High risk lesions"
Proliferative lesions — The degree of breast development appears to be important in the susceptibility to proliferative influences [51]. 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 [51]. 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 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 [52,53], and the site of origin of ductal carcinomas (picture 13 and picture 14 and picture 15 and picture 16):

● In autopsy studies, the nontumoral parenchyma of breasts harboring a malignancy contains a significantly higher number of hyperplastic terminal ducts, atypical type one lobules, and ductal carcinoma in situ (DCIS) originating from type 1 lobule compared to those breasts that are free of malignancy [35,46]. 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 lobule, 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) consist of predominantly type 1 lobules [46,54].

● 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 [10,45]. 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 [10]. (See 'Menopause' above.)

More differentiated lobular structures, such as type 2 lobules, are affected by other types of neoplastic lesions, notably lobular carcinomas (picture 17) [35].

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 protooncogenes 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 "BRCA1 and BRCA2: Prevalence and risks for breast and ovarian cancer"). 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 benz[a]pyrene [55]. 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 [56]. 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 ER and PR 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 [30,57]. 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 rather than hormone receptor content, similar to what has been observed with chemical carcinogenesis [38,58,59]. The independence of ER 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 [60,61].

- 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 [45,47]. (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
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- Basics topics (see "Patient information: Normal sexual development (puberty) (The Basics)" and "Patient information: Early puberty (The Basics)" and "Patient information: Late puberty (The Basics)"

**SUMMARY**

- 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.)

- Breast tissue is composed of both epithelial and stromal elements. The epithelial components are branching ducts which 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 non-lactating state, is composed of adipose and fibrous connective tissue. (See 'Anatomy' above.)

- 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 'Anatomy' above.)

- 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 'Anatomy' above.)

- 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.)

- 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 'Pregnancy and lactation' above.)

- 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.)

- 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 'Menopause' above.)

- 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.)

- The extent of breast involution appears to influence the risk of breast cancer, and may modify other breast cancer risk factors, including parity. (See 'Parity, lobular differentiation and breast cancer risk' above.)

- 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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INTRODUCTION — Benign breast disease represents a spectrum of disorders that come to clinical attention as imaging abnormalities or as palpable lesions found on physical examination. Following establishment of a benign diagnosis, treatment in general is aimed at symptomatic relief and patient education.

Some benign breast diseases, such as atypical hyperplasia, confer an increase in the patient’s future risk of developing breast cancer, and should lead to counseling about screening recommendations and risk reduction.
strategies. These lesions are considered risk markers, rather than premalignant, because those cancers that subsequently develop are not necessarily in the area of the atypia, and may occur in the contralateral breast.

This topic will review the pathologic classification and treatment of benign breast disorders. Evaluation of women presenting with symptoms related to the breast and diagnosis of breast disorders are discussed separately. (See "Clinical manifestations and diagnosis of a palpable breast mass" and "Breast pain" and "Nipple discharge".)

CLASSIFICATION OF BENIGN BREAST LESIONS — Benign epithelial breast lesions can be classified histologically into three categories: nonproliferative, proliferative without atypia, and atypical hyperplasia. The categorization is based upon the degree of cellular proliferation and atypia [1-10]. (See "Breast development and morphology".)

NONPROLIFERATIVE BREAST LESIONS — Nonproliferative epithelial lesions are generally not associated with an increased risk of breast cancer [1]. It should be noted that terms such as fibrocystic changes, fibrocystic disease, chronic cystic mastitis, and mammary dysplasia refer to nonproliferative lesions and are not useful clinically, as they encompass a heterogeneous group of diagnoses [5,11]. The most common nonproliferative breast lesions are breast cysts. Other nonproliferative lesions include papillary apocrine change, epithelial-related calcifications and mild hyperplasia of the usual type [5].

Simple breast cysts — Simple cysts are fluid filled, round or ovoid masses derived from the terminal duct lobular unit. Breast cysts can present as breast masses or mammographic abnormalities. Cysts are common in women between 35 and 50 years old. Acute enlargement of cysts may cause severe, localized pain of sudden onset. The diagnosis and management of breast cysts is discussed elsewhere. (See "Breast cysts: Clinical manifestations, diagnosis, and management".)

Papillary apocrine change — Papillary apocrine change is a proliferation of ductal epithelial cells showing apocrine features, characterized by eosinophilic cytoplasm [5].

Epithelial-related calcifications — Epithelial related calcifications are benign calcifications that are observed in breast tissue and can be seen in normal ducts and lobules, breast stroma or blood vessel walls [5].

Mild hyperplasia of the usual type — Mild hyperplasia of the usual type is an increase in the number of epithelial cells within a duct that is more than two, but not more than four, cells in depth [5]. The epithelial cells do not cross the lumen of the involved space.

PROLIFERATIVE BREAST LESIONS WITHOUT ATYPIA — Proliferative lesions without atypia include usual ductal hyperplasia, intraductal papillomas, sclerosing adenosis, radial scars and fibroadenomas. These lesions are
associated with a small increased risk of developing breast cancer, approximately 1.5 to 2 times that of the general population [2-5,8,9,12-15]. Fibroadenomas are included in this category, but it is important to note that the histologic features of the fibroadenoma influence the risk of breast cancer. The risk of subsequent breast cancer is slightly elevated only if the fibroadenoma is complex, if there is adjacent proliferative disease or if there is a family history of breast cancer. For the majority of women with simple fibroadenomas, there is no increased risk of developing breast cancer [2-5,12].

**Usual ductal hyperplasia** — Ductal hyperplasia without atypia is a pathologic diagnosis, usually found as an incidental finding on biopsy of mammographic abnormalities or breast masses, characterized by an increased number of cells within the ductal space. Although the cells vary in size and shape, they retain the cytological features of benign cells [5,6]. No additional treatment is needed for ductal hyperplasia. The risk of subsequent breast cancer in women with usual ductal hyperplasia is small and chemoprevention is not indicated.

**Intraductal papillomas** — Solitary intraductal papillomas may be identified as a mass on a mammogram (image 1), ultrasound (image 2), MRI (image 3), ductogram [16], or incidental [17]. Nipple discharge is a frequent clinical presentation. (See "Nipple discharge".) Solitary papillomas consist of a monotonous array of papillary cells that grow from the wall of a cyst into its lumen. Solitary papillomas can harbor areas of atypia or ductal carcinoma in situ (DCIS). Although there is some debate in the literature, the standard management of papillomas diagnosed by CNB is surgical excision [14,18-23]. In a metaanalysis of 34 studies that included 2236 nonmalignant breast papillary lesions diagnosed by CNB, 346 nonmalignant papillomas (15.7 percent) were upgraded to malignancy following a surgical excision [23]. The diagnosis of malignancy is even higher when the papilloma contains atypical cells (see 'Management of atypical lesions on core biopsy results' below). However, if an intraductal papilloma is incidental and ≤2 mm, an excision may not be necessary. In a retrospective review of 36 patients who underwent a core breast biopsy for calcifications or a mass and an intraductal papilloma was identified incidental to the mammographic finding, no cancers were identified in 14 patients who underwent an excision [17]. The remaining 24 patients were radiographically stable for over 12 months. Larger studies should be performed to determine if no excision can be recommended for incidental intraductal papillomas.

Once the diagnosis of solitary papilloma is confirmed by excisional biopsy, no additional treatment is needed. Unless there is associated atypia, there is no increased risk of subsequent breast cancer. (See 'Atypical hyperplasia' below.)
Multiple papillomas — Diffuse papillomatosis (multiple papillomas) may present as breast masses, nodules on ultrasound, or may be the cause of nipple discharge and can be seen on ductography. Diffuse papillomatosis is defined as a minimum of five papillomas within a localized segment of breast tissue [20,24]. After excision, additional treatment is not needed for diffuse papillomatosis. The risk of subsequent breast cancer in women with diffuse papillomatosis is small and chemoprevention is not indicated.

Sclerosing adenosis — Sclerosing adenosis is a lobular lesion with increased fibrous tissue and interspersed glandular cells. It can present as a mass or a suspicious finding on mammogram [25,26]. No treatment is needed for sclerosing adenosis. The risk of subsequent breast cancer in this population is small and chemoprevention is not indicated.

Radial scars — Radial scars, also called complex sclerosing lesions, are a pathologic diagnosis, usually discovered incidentally when a breast mass or radiologic abnormality is removed or biopsied. Occasionally, radial scars are large enough to be detected by mammography, which cannot reliably differentiate between these lesions and spiculated carcinoma [27-30]. Radial scars are characterized microscopically by a fibroelastic core with radiating ducts and lobules. There is ongoing controversy about the need for surgical excision when radial scars are found on core biopsy [31,32]. We suggest that these be excised since most series show that 8 to 17 percent of surgical specimens at subsequent excision are positive for malignancy [33-37]. In addition to the possibility of finding an unrecognized in situ or invasive component, there is some evidence that radial scars may be premalignant lesions, meaning that they can slowly progress from scar to hyperplasia to carcinoma over time [38]. No additional treatment beyond excision is needed for radial scars. The risk of subsequent breast cancer after excision in this population is small and chemoprevention is not indicated.

Simple fibroadenomas — Simple fibroadenomas are benign solid tumors containing glandular as well as fibrous tissue. In 20 percent of cases, multiple fibroadenomas occur in the same breast or bilaterally. The etiology of fibroadenomas is not known but a hormonal relationship is likely since they persist during the reproductive years, can increase in size during pregnancy or with estrogen therapy, and usually regress after menopause. They are most commonly found in women between the ages of 15 and 35 years [39]. Although originally classified as nonproliferative lesions, fibroadenomas are now considered proliferative breast lesions [12]. However, it is important to note that the histologic features of the fibroadenoma influence the risk of breast cancer. The risk of subsequent breast cancer is slightly elevated only if the fibroadenoma is complex, if there is adjacent
proliferative disease or if there is a family history of breast cancer. For the majority of women with simple fibroadenomas, there is no increased risk of developing breast cancer [2-5,12]. Fibroadenomas usually present as a well-defined, mobile mass on physical examination or a well-defined solid mass on ultrasound. A well-defined solid mass with benign imaging features can be managed with core needle biopsy or short-term (three to six months) follow-up with a repeat ultrasound and breast examination [40]. Definitive diagnosis can only be confirmed with a core biopsy or excision.

It is not necessary to excise all biopsy proven fibroadenomas. Disadvantages of excisional surgery include scarring at the incision site, dimpling of the breast from the removal of the tumor, damage to the breast's duct system, and mammographic changes (e.g., architectural distortion, skin thickening, increased focal density). If a biopsy proven fibroadenoma is asymptomatic, then it can be left in place, although some women wish to have the mass excised so that they will not worry further. Cryoablation is an alternative to surgical excision of fibroadenomas, but should only be considered after a core biopsy diagnosis of fibroadenoma has been made [41-45]. A multicenter trial of 50 patients who underwent office-based cryoablation under ultrasound guidance reported the lesions tended to disappear progressively [42] and 75 percent were not palpable at 12 months follow-up [43]. Transient side effects included ecchymosis, local swelling, and discomfort that lasted as long as a few weeks after treatment. Percutaneous vacuum-assisted ultrasound-guided excision is another alternative to open excision technique for removal of fibroadenomas, but may be less effective for lesions >2 cm [46].

If a presumed fibroadenoma increases in size or is symptomatic, then excision is mandated to rule out malignant change and confirm the diagnosis [41,42,46]. Rapid growth of a lesion raises the suspicion for a phyllodes tumor, unusual fibroepithelial tumors which require more extensive surgical resection and in some cases may require radiation treatment as well.

**ATYPICAL HYPERPLASIA** — Atypical hyperplasia (AH) includes both ADH and ALH. AH is a pathologic diagnosis, usually found as an incidental finding on biopsy of mammographic abnormalities or breast masses. These lesions have some, but not all, of the features of ductal carcinoma in situ (DCIS) or lobular carcinoma in situ (LCIS).

- Atypical ductal hyperplasia — Atypical ductal hyperplasia (ADH) is characterized by a proliferation of uniform epithelial cells with monomorphic round nuclei filling part but not the entire involved duct.

ADH shares some of the cytologic and architectural features of low-grade
ductal carcinoma in situ (DCIS) [5]. (See "Breast ductal carcinoma in situ: Epidemiology, clinical manifestations, and diagnosis").

- Atypical lobular hyperplasia – Atypical lobular hyperplasia (ALH) is characterized by monomorphic, evenly spaced, dyshesive cells filling part, but not all, of the involved lobule. ALH can also involve ducts.

ALH shares some of the cytologic and architectural features of lobular carcinoma in situ (LCIS) [5].

Atypical hyperplasias (ADH and ALH), especially multifocal lesions, confer a substantial increase in the risk of subsequent breast cancer (relative risk 3.7 to 5.3) [3,4,7,13,47]. AH is associated with an increased risk of both ipsilateral and contralateral breast cancer and thus provides evidence of underlying breast abnormalities that predispose to breast cancer [4]. In a report from the Nurses' Health Study, only 56 percent of cancers that developed in women with AH occurred in the ipsilateral breast [48]. The cumulative incidence of breast cancer over 30 years approached 35 percent.

Some studies have shown that the risk of developing breast cancer is higher with ALH than ADH, however the data on this are conflicting [13,47-49]. There is a higher risk of subsequent breast cancer when the ALH involves both lobules and ducts (relative risk 6.8) as compared to lobules alone (relative risk 4.3) or ducts alone (2.1) [50].

Data on the effect of family history of breast cancer in women with atypical hyperplasia are conflicting [51]. Several studies showed that a family history of breast cancer substantially increased the breast cancer risk in women with AH [4,49]. However, subsequent studies have not confirmed this and did not show that a family history further increased the breast cancer risk in women with AH [4,47,51].

**Risk reduction strategies for women with atypical hyperplasia** — Women with AH should be counseled regarding risk reduction strategies. Ongoing surveillance with yearly mammography and twice-yearly breast exams is appropriate [2,3,8,9,12-14]. Women with AH should stop taking oral contraceptives, avoid hormone replacement therapy, and make appropriate lifestyle and dietary changes. (See "Factors that modify breast cancer risk in women").

Primary prevention with the selective estrogen receptor modulators tamoxifen or raloxifene, or an aromatase inhibitor may be considered in women with AH for breast cancer risk reduction, although the benefits and
risks must be discussed thoroughly. The Gail model incorporates atypical proliferative disease into a risk calculation that can be used to identify women who are appropriate candidates for primary prevention of breast cancer. The tool can be accessed online at www.cancer.gov/bcrisktool. The topics of breast cancer risk assessment and risk reduction are discussed in detail elsewhere. (See "Factors that modify breast cancer risk in women" and "Selective estrogen receptor modulators and aromatase inhibitors for breast cancer prevention" and "Patient information: Medications for the prevention of breast cancer (Beyond the Basics)".)

**FLAT EPITHELIAL ATYPIA** — Flat epithelial atypia is a separate entity from ADH or ALH. Flat epithelial atypia is sometimes referred to as columnar cell change with atypia or columnar cell hyperplasia with atypia. Typically, flat epithelial atypia is diagnosed on breast biopsies done for calcifications found on screening mammograms. The relationship between flat epithelial atypia and cancer is still being defined, but the available data suggest that the risk of local recurrence or progression to invasive cancer is low [52,53]. (See "Atypia and lobular carcinoma in situ: High risk lesions of the breast", section on 'Flat epithelial atypia (FEA').)

**MANAGEMENT OF ATYPICAL LESIONS ON CORE BIOPSY**

**RESULTS** — If the core needle biopsy (CNB) identifies an abnormality, such as atypical ductal hyperplasia (ADH), atypical lobular hyperplasia (ALH), flat epithelial atypia, lobular carcinoma in situ (LCIS), papilloma, complex sclerosing adenosis or radial scar, a surgical excision should be performed to avoid underestimation of the diagnosis [54-60]. (See 'Proliferative breast lesions without atypia' above.) Based upon retrospective reviews, analysis of a larger tissue sample removed by a surgical excision results in an upgrade in diagnosis from atypia to ductal carcinoma in situ (DCIS) or invasive breast cancer in 10 to 30 percent of patients [54,59-64]. (See "Atypia and lobular carcinoma in situ: High risk lesions of the breast", section on 'Surgical management of AH'.) In addition, an intraductal papilloma with atypia diagnosed by CNB is associated with a high underestimation of malignancy. In the metaanalysis previously described where a surgical excision was performed following a CNB, atypical papillary lesions were significantly more likely to be associated with malignancy compared with papillary lesions without atypia (36.9 versus 7.0 percent) [23]. (See 'Intraductal papillomas' above.)

**MISCELLANEOUS LESIONS OF THE BREAST**

**Lipoma** — Breast lipomas are benign, usually solitary tumors composed of mature fat cells. These present as soft, nontender, well-circumscribed masses. Clinically, it is sometimes difficult to distinguish lipomas from other conditions; the diagnosis can be confirmed with a core or excisional biopsy. Core biopsies are somewhat problematic for lipomas, as it is
difficult to be certain that the diagnosis is concordant, and lipomas should be surgically excised if they cause diagnostic confusion, continue to enlarge, or grow rapidly [6]. For smaller lesions, excisional biopsy is often preferable. There is no increased risk of subsequent breast cancer associated with lipomas.

**Fat necrosis** — Fat necrosis of the breast is a benign condition that most commonly occurs as the result of breast trauma or surgical intervention. Fat necrosis can be confused with a malignancy on physical examination and may mimic malignancy on radiologic studies. It is sometimes necessary to biopsy these lesions to confirm the diagnosis, although experienced radiologists can usually determine that a lesion represents fat necrosis based on mammographic and ultrasound findings such as oil cysts (collections of liquefied fat) [6,65]. Once the diagnosis is established, excision is not necessary and there is no increased risk of subsequent breast cancer.

**Giant fibroadenomas** — Giant fibroadenomas refer to histologically typical fibroadenomas over 10 cm in size [5]. Excision is recommended. The primary challenge for the pathologist is to differentiate these from phyllodes tumors. Phyllodes tumors have a more cellular stromal component than fibroadenomas.

**Juvenile fibroadenomas** — Juvenile fibroadenomas are distinguished from adult fibroadenomas by exhibiting more glandularity and greater stromal cellularity. They occur in young women between the ages of 10 and 18 and vary in size from 5 to 20 cm in diameter. These usually painless, solitary, unilateral masses grow rapidly. Excision is recommended, but there is a risk of damage to the breast bud in prepubertal girls, and this should be discussed with the patient and family [5,66].

**Complex fibroadenomas** — Complex fibroadenomas present as a mass on physical examination or a nodule on mammogram or ultrasound. However, on pathology, these contain other proliferative changes, such as sclerosing adenosis, duct epithelial hyperplasia, epithelial calcification, or papillary apocrine changes [67]. They are associated with a slightly increased risk of cancer when multicentric proliferative changes are present in the surrounding glandular tissue.

Appropriate management of complex fibroadenomas is controversial. While some believe that complex fibroadenomas warrant complete removal for histological examination, others suggest that they can be managed conservatively following core biopsy [67]. In one series of 401 fibroadenomas, 63 (15.7 percent) were considered complex. At a mean follow-up of two years, invasive carcinoma was found in only one of the 63 patients with complex fibroadenomas; her initial core biopsy had shown atypical lobular hyperplasia.

**Diabetic mastopathy** — Diabetic mastopathy, also known as lymphocytic
mastitis or lymphocytic mastopathy, is seen occasionally in premenopausal women who have longstanding type 1 diabetes mellitus. The typical presentation is a suspicious breast mass with a dense mammographic pattern. Core biopsy is recommended for diagnostic confirmation. Pathology shows dense keloid-like fibrosis and periductal, lobular, or perivascular lymphocytic infiltration [68-70]. The pathogenesis is unknown, but it may represent an autoimmune reaction as the histologic features are similar to those seen in other autoimmune diseases [71]. Once the diagnosis is established, excision is not necessary and there is no increased risk of subsequent breast cancer.

**Galactocele** — Galactoceles (milk retention cysts) are cystic collections of fluid, usually caused by an obstructed milk duct. These present as soft cystic masses on physical exam. At mammography, galactoceles may appear as an indeterminate mass, unless the classic fat-fluid level is seen. Ultrasound may show a complex mass. Diagnosis can be made based on the clinical history and aspiration, which yields a milky substance [72]. Once diagnosis is established, excision is not necessary and there is no increased risk of subsequent breast cancer. (See "Common problems of breastfeeding and weaning").

**Hamartoma** — Hamartomas are benign lesions, also known as fibroadenolipoma, lipofibroadenoma, or adenolipoma [73]. Hamartomas have varying amounts of glandular, adipose, and fibrous tissue. They present as discrete, encapsulated, painless masses, or are found incidentally on screening mammography. The diagnosis can be difficult to make with limited tissue, as hamartomas do not have specific diagnostic features. Fine needle aspiration and core needle biopsy are not sufficient to establish the diagnosis. As coexisting malignancy can occur; excision is recommended [6].

**Adenoma** — Adenomas are pure epithelial neoplasms of the breast. They are distinguished from fibroadenomas by their sparse stromal elements. Adenomas are divided into two main groups: tubular and lactating adenomas. Lactating adenomas occur commonly in pregnancy. They are well circumscribed and lobulated. Although they may require excision because of their size, they do not have malignant potential [5,6].

**Idiopathic granulomatous mastitis** — Idiopathic granulomatous mastitis (IGM) is an inflammatory mass in the breast. The symptoms and radiologic findings may be mistaken for nonpuerperal mastitis, a breast abscess, or most often, carcinoma. Biopsy is necessary to make a diagnosis. IGM is discussed in more detail elsewhere. (See "Mastitis and other skin disorders of the breast in adults").

**Pseudoangiomatous stromal hyperplasia** — Pseudoangiomatous stromal hyperplasia (PASH) is a benign stromal proliferation that simulates a vascular lesion [5]. PASH may present as a mass or thickening on physical
examination. The most common appearance on mammography and ultrasound is a solid, well-defined, noncalcified mass [74]. The characteristic histologic appearance is a pattern of slit-like spaces in the stroma between glandular units [75]. PASH can be confused with mammary angiosarcoma [6,76]. If there are any suspicious features on imaging, the diagnosis of PASH on a core biopsy should not be accepted as a final diagnosis, and excisional biopsy should be performed. However, in the absence of suspicious imaging characteristics, a diagnosis of PASH at core biopsy is considered sufficient, and surgical excision is not always necessary [77]. There is no increased risk of subsequent breast cancer associated with PASH.

**Sarcoidosis** — Breast symptomatology in sarcoidosis is rare and seen primarily in patients with systemic involvement. Sarcoidosis of the breast presents as firm hard masses, mimicking carcinoma. The mammographic appearance is also suspicious with irregular, ill-defined, spiculated masses that are solid on ultrasound. Biopsy is needed for confirmation of diagnosis [78,79]. There is no increased risk of subsequent breast cancer associated with sarcoidosis of the breast. (See "Clinical manifestations and diagnosis of pulmonary sarcoidosis".)

**Nipple Discharge** — Discharge is considered pathologic if it is spontaneous, persistent, or arises from a single duct. It is also pathologic if the discharge contains gross or occult blood. This topic is discussed in detail separately. (See "Nipple discharge".)

**Breast Pain** — Breast pain is classified as cyclical (ie, related to the menstrual cycle), noncyclical, or extramammary. Breast cancer may present as breast pain, thus a full evaluation is indicated. This topic is discussed in detail separately. (See "Breast pain".)

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- Beyond the Basics topics (see "Patient information: Common breast
SUMMARY AND RECOMMENDATIONS

- Benign breast lesions can be classified into three categories based on histologic findings: nonproliferative, proliferative without atypia, and atypical hyperplasias. (See 'Classification of benign breast lesions' above.)

- Nonproliferative lesions are not associated with an increased risk of breast cancer. Management is directed at making a definitive diagnosis and providing relief of symptoms. (See 'Nonproliferative breast lesions' above.)

- Proliferative disease without atypia is associated with a small increased risk of subsequent breast cancer. Once the diagnosis is established, no additional treatment is indicated. (See 'Proliferative breast lesions without atypia' above.)

- Atypical ductal hyperplasia and atypical lobular hyperplasia are associated with a substantial increase in risk of subsequent breast cancer. Women with atypical hyperplasia should be closely monitored and counseled regarding risk reduction strategies. (See 'Atypical hyperplasia' above.)

- For patients with a proliferative breast lesion identified on core needle biopsy, such as atypical hyperplasia, lobular carcinoma in situ (LCIS), or an intraductal papilloma, we perform a surgical excision to avoid underestimation of a malignant diagnosis. (See 'Management of atypical lesions on core biopsy results' above and "Atypia and lobular carcinoma in situ: High risk lesions of the breast".)