Benign Breast Diseases

Article *in* Journal of Mammary Gland Biology and Neoplasia · November 2005

DOI: 10.1007/s10911-006-9006-4 · Source: PubMed

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DOI 10.1007/s10911-006-9006-4

REVIEW ARTICLE

Benign Breast Diseases

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Published online: 10 August 2006

Abstract Benign breast diseases have always been neglected in comparison to cancer, despite the fact that there are many more patients with such diseases than patients presenting to a breast clinic for cancer. Like normal breast tissues, benign breast diseases are under a complex system of controls by both systemic hormonal and local factors. In this review, we attempt to present an overview of the latest knowledge concerning the epidemiology, classification, clinical presentation, management, and physiopathology of these disorders.

Keywords Benign breast tumors · Estradiol · Prolactin · Growth factors

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Introduction

Benign breast diseases (BBD) have always been neglected in comparison to cancer, despite the fact that there are many more patients with such diseases than patients presenting to a breast clinic for cancer. So far, BBD have been the subject of a relatively few isolated and unconnected studies, and earlier related work has often been ignored. This situation has led to a great deal of confusion, especially because different authors have their own nomenclature for benign lesions of the breast, and, unfortunately, a unique and unequivocal definition has not yet been commonly accepted. Hence, it is even more difficult to find in the literature data concerning the mechanisms involved in the development of such disorders.

Breast tissues are under a complex system of control by systemic factors, particularly hormones acting through their respective receptors, as well as a number of local factors. These include paracrine hormones, released by one type of cell to influence adjacent cells of similar or differing function; juxtacrine factors, situated on the surface of the producing cell to influence adjacent cells by direct contact; and autocrine hormones, which act on the same cell by intracellular or

surface receptors. All of these hormones interact, as is true for systemic hormones, by influencing locally derived factors—cell adhesion-related proteins as well as autocrine and paracrine hormones—to produce signal pathways that finally result in cell regulation and stimulation.

In this review, we attempt to present an overview of the latest knowledge concerning the epidemiology, classification, clinical presentation, management, and physiopathology of benign breast disorders.

Epidemiology

Classification

The term "BBD" includes a large number of physiopathological lesions of the different components (epithelial, stromal, adipocytes, or vascular) of the breast. The classification and analysis of BBD have long been controversial due to the lack of clear-cut clinical and histopathological separation between the physiologic and pathologic changes in the breast [1]. Much of the controversy concerns the relationship between BBD and the subsequent development of carcinoma. Two major dates have been of great importance in the comprehension and classification of the benign disorders.

The first, 1985, represents the histological classification based on the work of Dupont and Page [2] which was adopted at the consensus meeting of the College of American Pathologists. The concept of benign epithelial proliferative disease identifies the histological characteristics of BBD that have a cancerous potential. Three groups of BBD have been specified; non-proliferative lesions, proliferative lesions without atypia, and lesions with atypical hyperplasia.

The second, 1987, corresponds to the ANDI (Aberrations of Normal Development and Involution) classification of benign breast disorders, which provides an overall framework for benign conditions of the breast encompassing both pathogenesis and degree of abnormality (Table 1) [3]. This classification states that breasts are under endocrine control and show a wide range of appearances during reproductive life. For example, microcysts must be regarded as normal, and macrocysts are at most an aberration of normality and should not be considered as a disease.

Unfortunately, most epidemiological studies have not used these new classifications. Thus, the two major conditions most often described in the epidemiological literature are fibroadenoma and fibrocystic disease. It would also be important to include severe mastalgia as a first stage of BBD and as a potential link to subsequent breast cancer [4, 5].

Incidence of BBD

Benign breast disease incidence is generally not well-estimated. Indeed, BBD is not always symptomatic, and most of the women do not come in for medical consultation. Women presenting with a well-defined clinical, cytological, or histological diagnosis represent a selected subgroup of all cases. However, the incidence of BBD can be estimated by its prevalence rates in autopsy studies, as well as its cumulative incidence rates from cohort studies.

In a recent review of post-mortem studies, Goehring and Morabia [6] estimate that about one out of two women develops some degree of fibrocystic breast disease during her lifetime, and one out of five women develops fibroadenoma. In contrast, from cohort studies data, the cumulative incidence of biopsy-proven fibrocystic breast disease before the age of 65 years was 8.8%; the corresponding cumulative incidence of fibroadenoma was 2.2%. Thus, compared with autopsy studies, only 10–20% of BBD are histologically diagnosed. Therefore, interpreting epidemiological studies related to pathologically proven BBD is difficult, since the cases included in the studies might be restricted to the most clinically significant lesions.

One of the most comprehensive ways to comprehend BBD is to understand the evolution of breast structure throughout life [7]. Each phase presents its own mechanisms, and if any abnormality occurs, a specific BBD might develop.

Table 1 Classification of benign breast disease phenotypes.

Stage	Normal process	Aberration	Disease
Early reproductive (15–25 years)	Lobular development	Fibroadenoma	Giant fibroadenoma Multiple fibroadenomas
Mature reproductive (25–40 years)	Cyclical changes during menstruations	Cyclical mastalgia Nodularity	Incapacitating mastalgia
Involution (35–55 years)	Lobular involution	Macrocysts Sclerosing lesions	Periductal mastitis
	Epithelial turnover	Simple epithelial hyperplasia	Epithelial hyperplasia with atypia

Development and Physiology of the Normal Human Breast: The Impact of Lifetime Changes

The main feature of breast development between 15 and 25 years of age is the addition of lobular structures to the already developing duct system. Until the age of about 35 years, the luteal phase is also associated with enhanced acinar sprouting from the ductules. Both epithelial and stromal elements of the lobule are under hormonal control, and there is evidence that the two work in tandem [7]. It is likely that interference with these close interactions may be responsible for many of the conditions that are often included under the term "BBD". The repeated development and involutional changes of menstruation and pregnancy, occurring between 15 and 50 years of age, create abundant opportunities for minor aberrations to occur.

This risk is increased by the fact that it overlaps for more than 20 years with involution, which takes place between 35 and 55 years of age. Involution affects the lobules and is highly dependent on the relationship between the epithelium and specialized stroma of the lobule [7]. During this process of lobular involution, the loose hormone-responsive intralobular connective tissue is replaced by the more standard interlobular type of fibrous tissue. Eventually, by the time menopause has been reached and passed, involution is extensive, with only a few ducts remaining and few if any lobular structures. Should the stroma disappear too early, the epithelial acini remain and may form microcysts, which are obviously a prime target for macroscopic cyst formation. Most benign disorders derive from those normal processes of reproductive life. The ANDI classification (Table 1) places these disorders in a spectrum ranging from normal, through slight abnormality (aberration), to disease, and takes into account the transformations occurring throughout life.

Disorders of Development: Fibroadenomas

Pathogenesis

Fibroadenomas (FAs) are benign tumors of the breast typically composed of stromal and epithelial cells. Since they arise from lobules, it is not surprising that these are seen predominantly in women in the 15–25 age group, even though they may be diagnosed later. FA should not be regarded as a neoplasm. Parks [8] showed that hyperplastic lobules, histologically identical to clinical FA, are present so commonly as to be regarded as normal, and can probably be found in all breasts if they are sought with sufficient care. All the cellular elements of FA are normal, and epithelium and myoepithelium maintain a normal relationship. Molecular biology studies have shown that FAs are polyclonal, consistent with hyperplasia, in contrast to phyllodes tumors which are monoclonal, consistent with a neoplastic condition [9]. It is not clear whether this is a secondary change in a FA, or is present in a phyllodes tumor de novo.

FAs usually grow to 1 or 2 cm in diameter and then stay constant in size. Rarely will a FA continue to grow to a size of 3 cm, although this is sufficiently common to be regarded as within the normal spectrum. Growth beyond 5 cm is sufficiently uncommon as to justify being regarded as a disease, known as giant FA. Similarly, multiple FA (defined by more than 3 or 5 lesions in one breast, depending on authors) are so uncommon, and their implications are so uncertain, as also to justify being considered a disease [10]. However, no evidence exists for or against the supposition that giant FA arise from the continued progression of small FA, i.e., that aberration progresses to disease. It is possible that giant FA is a separate condition de novo, or an added factor may lead to progression from a "standard" FA.

Mechanisms controlling FA development and growth are poorly understood. In addition to the role of estrogen and progesterone receptors expressed by epithelial cells, recent studies describe a possible role for growth factors and their receptors in the pathogenesis and growth of BBD, including FA, suggesting that multiple receptor signaling pathways could be involved in the growth and differentiation of benign breast lesions [11]. However, concerning the risk of development of subsequent breast cancer, a large retrospective study [12] has concluded that there is no increased risk for a woman with a simple FA and no family history of breast cancer.

Clinical Features and Management

In young women, the clinical features are very characteristic [13]. The FA is smooth, round or lobulated, firm with discrete swelling and high mobility. This last feature is due to encapsulation and to the softness of the breast at this age. The clinical presentation of FA in an older woman is much less characteristic, because of the involutional fibrotic changes, and cancer must be excluded unequivocally.

Mammography is not indicated in young women, before 35 years, with dense breasts. In older patients, FA can be seen as a solid smooth lesion, of similar density to the surrounding breast when small, and more dense when large. FA may present a smooth border outlined by the mammary fat. It may look identical to a cyst, but needle aspiration will easily differentiate the two. In the postmenopausal period, half of the FA will show typical stippled "pop-corn" calcification (Fig. 1b).

Ultrasonography is the best imaging method in young women. The ultrasonic features include oval sharp contour, weak internal echoes in uniform distribution and interme-

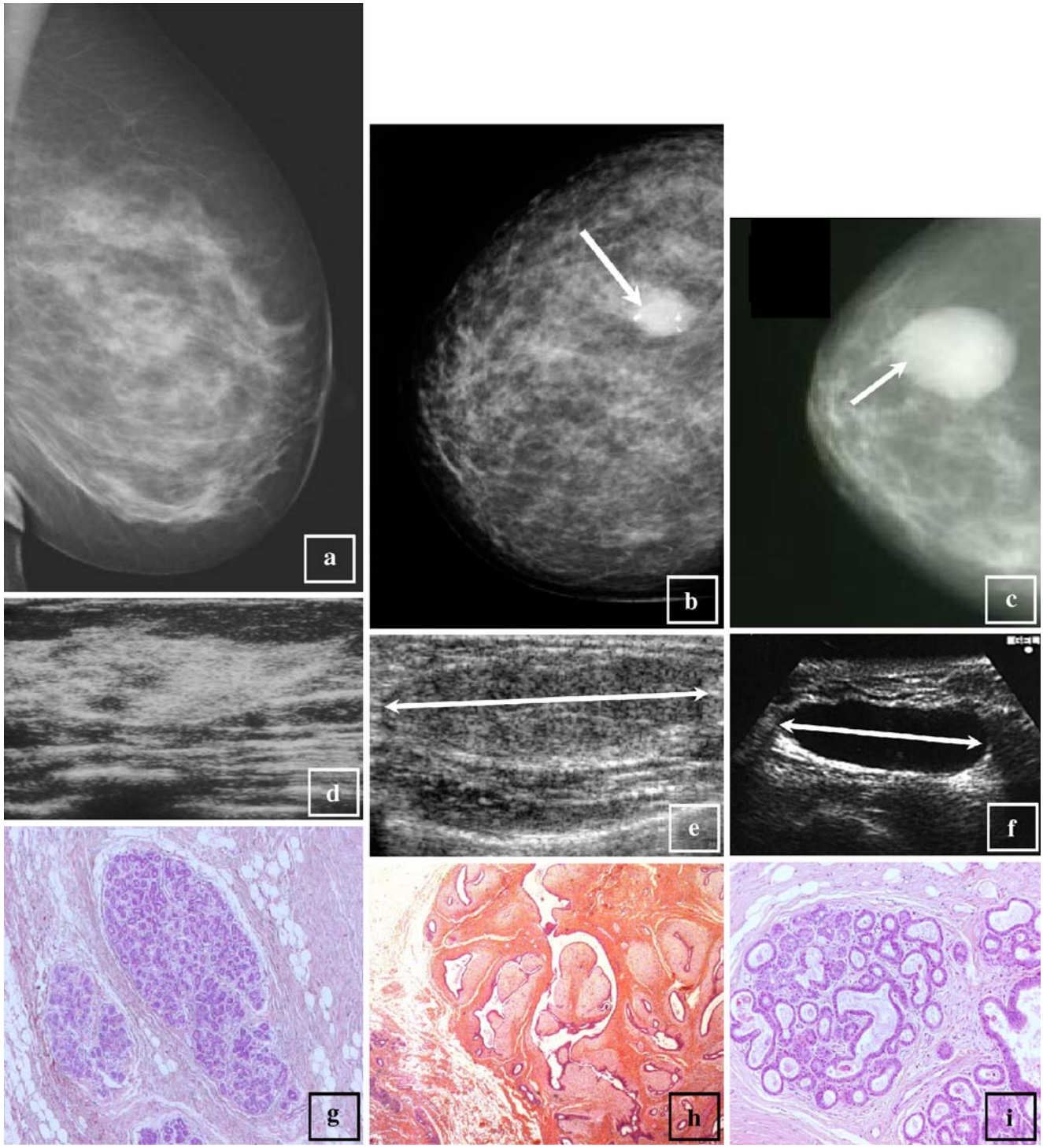

Figure 1 *Mammography.* **a** Normal breast—dense glandular tissue and fat are visible in this breast, skin is thin, and no lesion is visible within the subcutaneous fat. **b** Fibroadenoma—a smooth contour homogeneous mass is visible in the outer quadrant of the breast; *popcorn-like calcifications* are visible within the mass (*arrow*). **c** Cyst—*tea cup calcifications* are visible in the mass, corresponding to calcic milk within the cyst (*arrow*). *Ultrasonography.* **d** Normal breast—hyperechoic tissue corresponds to glandular tissue and hypoechoic tissue depicts fat; in this breast, glandular tissue is predominant. **e** Fibroadenoma—an *oval nodule* is visible in the breast; regular contour, homogeneous content, and hyperechoic internal septa are typical of a benign lesion. **f** Cyst—an *oval shaped*, anechoic lesion with a thin wall is typical of a benign cyst. *Histology.* **g** Normal aspect of a breast lobular unit. **h** Fibroadenoma. **i** Cysts developed in the terminal ductal lobular unit (TDLU).

diate attenuation [14]. Typically, the ovoid smooth mass is narrower in its anteroposterior than in its transverse diameter (Fig. 1e).

The cytological appearance of FA is typical. The epithelium forms broad sheets that are uniform, equally spaced, and cohesive. Cohesive cells typically show branching epithelial structures, resembling "antler horns," and bare nuclei are evident. Cytology is not necessary in a woman younger than 25 years with a typical FA, but fine needle aspiration biopsy (or even core needle biopsy) is imperative when the features are not all typical and if the woman is older than 25 [13].

Concerning the treatment, the conservative approach is acceptable at any age if there has been a triple assessment unequivocally benign, with a core needle biopsy providing definitive histology after 25 years. Otherwise, if any feature is atypical or if the patient wishes to get rid of it, surgery is indicated. There has been a tendency in Europe to treat FA with hormonal therapy (progestogens, tamoxifen), but the results have only been partially assessed [13, 15].

Histology

The macroscopic appearance of a FA is a sharply demarcated rounded or bosselated tumor, with a white glistening, bulging surface on section. It is easily enucleated from its pseudocapsule of compressed breast tissue to which it is attached.

The histological appearance is characteristic [13]. It consists of a combination of loose pale stroma and duct-like structures lined by regular epithelial cells (Fig. 1h). The tissues of a FA respond to external influences like the normal breast lobules. It will undergo hyperplastic changes during pregnancy, secrete milk during lactation, and involute at the menopause. There are a wide variety of histological changes that may be seen in typical FA. These include apocrine and squamous metaplasia, neither of which is significant. Marked hyperplasia of epithelial elements is also common, but does not reflect aggressive behavior. However, it may be an important cause of false-positive diagnosis of cancer on cytology.

Disorders of Cyclical Change: Mastalgia and Nodularity

Premenstrual enlargement and postmenstrual involution of the breast occurring with each cycle is so commonly associated with discomfort and nodularity as to lie within the spectrum of normality. A duration of painful nodularity of more than one week of the cycle is a useful definition for differentiation from normal discomfort, and the severity of the pain can be quantified with a pain chart. While no histological basis has been defined for these changes, the objection of such women to the concept of non-disease is supported by hormone studies, which show an underlying physiological abnormality demonstrated by excess prolactin release from the pituitary following stimulation of the hypothalamic pituitary axis [16]. It is likely that subtle stromal and epithelial changes accompany physiological variations in more severe cases of cyclical nodularity and mastalgia. Edema, stromal or lobular, can be demonstrated in the late cycle, but at present good evidence correlating this with clinical symptoms is lacking. Painful nodularity of the predominantly cyclical phase of the reproductive life (20–35 years) merges into and overlaps those symptoms which are more typically part of the involutional phase, especially cyst formation. While all have been lumped together as "fibrocystic disease" or "fibroadenosis" in the past, the clinical problems and management differ. Mammography or ultrasonography are necessary only in case of nodularity.

Disorders of Involution: Cyst Formation

Since the process of involution extends over 20 years of monthly cycles of mitosis and apoptosis, it is not surprising that a number of aberrations should arise involving different elements of the normal breast. It is interesting that the incidence of these changes is similar in a number of races with widely differing cancer incidences, supporting the "normal" view against the "precancerous" view.

Pathogenesis

The normal involution of the lobule is dependent on the continuing presence of the specialized stroma around it. If the stroma disappears too early, the epithelial acini remain and may form microcysts, setting the pattern for macrocyst development by obstruction of the efferent ductule. This concept of the macrocyst as being an involutional aberration rather than a disease, fits with its common occurrence and the fact that it is so frequently multiple and sub-clinical.

The current view is that all macrocysts start with an area of apocrine epithelium in a terminal ductal lobular unit (TDLU). Excessive secretion of the apocrine epithelium, probably compounded by osmotic effects of the secretion products, leads to progressive dilatation of the TDLU to give a microcyst. The dilatation is at first confined to the acini containing apocrine epithelium. This contrasts with involutional microcysts without apocrine epithelium. If the apocrine microcyst enlarges, it will become a macrocyst.

Cysts occur predominantly in the middle and late reproductive period, increasing in frequency from 35 years to a maximal incidence between 40 and 50 years. They

usually disappear after menopause, unless the patient is taking hormone replacement therapy.

Clinical Features and Management

Macroscopic cysts are usually asymptomatic, often discovered accidentally by the patient when touching her breast. In some case, they can be discovered because of sudden pain, probably due to sudden distension or to leakage of fluid into surrounding tissue, giving chemical irritation. There is no relation with the menstrual cycle, either for pain or for size. Nipple discharge is uncommon, but if found, it will be typical of cyst fluid.

Generally, a cyst is felt as a smooth, tense structure, readily palpable against the chest wall, and to some extent attached to breast tissue. Some cysts may be multilobular, while others are so tense that they feel hard or so large that they displace the Cooper's ligaments, producing apparent skin attachment or even retraction. The problem of diagnosis is solved by routine use of needle aspiration and ultrasonography [17].

A simple cyst on ultrasound is smooth in outline with a thin wall, has no internal echoes, and demonstrates posterior enhancement (Fig. 1f) [18]. However, in some cases, simple benign cysts do not have all these characteristics. It is important to evaluate the cyst wall carefully in two planes to look for projections in the cyst that may indicate the presence of an intracystic papilloma or papillary carcinoma. Simple cysts with the typical ultrasound findings do not need aspiration unless clinically indicated, but if there is any doubt as to whether the lesion is cystic, then aspiration is definitely indicated. Mammography is not indicated for the diagnosis of cysts, even though it can show calcifications (Fig. 1c). The treatment of cysts, if recurrent, is conservative. It consists of a complete aspiration of cyst fluid with a fine needle. The mass must disappear completely and, if it does not, it must be treated as any other persistent mass. The aspiration may be guided by sonography if necessary. Cytological examination is indicated only if the fluid is blood stained [19]. The hormonal background to cysts is not defined sufficiently to justify any form of hormone therapy on a routine basis.

Histology

The small cysts have no intrinsic significance except the potential to form larger cysts. They usually occur in clusters over an area of 2–3 cm and are blue colored. Larger cysts are thin walled and more brown, from the brownish opalescent fluid they contain. They are lined by a single layer of epithelium, or sometimes have no epithelial layer at all (Fig. 1i). The fluid content shows a wide range of appearances and consists of a variety of chemical substances. Cysts do not contain blood unless there is an associated neoplasm. Cyst fluid contains, among other biochemical products, hormones or growth factors in much higher concentrations than in blood, suggesting an active secretory process [20].

Other Benign Disorders of Ducto-glandular Tissue

Physiopathology

Some other conditions may be considered as aberrations of either the cyclical or the involution phases, such as sclerosing adenosis or epithelial hyperplasia. For example, sclerosing adenosis represents a complex histological picture, in which both proliferative and involutional changes are present. In clinical practice, women present with palpable lumps, with or without mastalgia. Epithelial hyperplasia is more complex. Some authors have shown that lobular and intraductal hyperplasia are common in the premenopausal period and tend to regress spontaneously after the menopause. However, studies by Dupont and Page [2] have shown that atypical lobular or ductal hyperplasias, particularly as seen in TDLU, are associated with breast cancer risk and should be considered as premalignant conditions.

Management

In any event, when a lump is felt in a woman's breast, a precise "triple" assessment must be performed. It is essentially clinical in the young woman, supplemented by ultrasound, cytology, or core needle biopsy if over 25 years of age. In a woman older than 35, mammography is also indicated. To avoid unnecessary biopsies, a well-defined approach must be taken to determine whether a mass is dominant and persistent. It is important to examine both breasts correctly during the first half of the menstrual cycle, to review the patient over a period of 2 months if needed, and to clearly define follow-up [21]. In the majority of cases, benign breast lesions present fairly characteristic mammographic appearances. They are usually smooth in outline and rounded, ovoid, or lobulated in shape. They might be single, but often are multiple and bilateral. There may be a surrounding halo of compressed fat, indicating that there is no infiltration. Breast structures are displaced rather than disrupted. Most are of equal-to-low density compared to the surrounding parenchyma. Fine microcalcifications occur in epithelial hyperplasia and sclerosing adenosis, and may cause diagnostic difficulties. Ultrasound in the evaluation of a palpable lump indicates if there is a lesion present or not and whether it is cystic or solid. The typical features of a benign solid mass are an ovoid smooth mass, narrower in its anteroposterior than in its transverse diameter, with even, low-level internal echoes. More than

precisely assessing a clinically palpable mass and allowing aspiration of cyst fluid, ultrasonography also helps guide fine needle aspiration or a biopsy. It is of major importance that in these cases, clinicians, radiologists, and pathologists work together.

Implications of Hormonal and Growth Factors in BBD Development

Implications of Steroid Hormones in BBD Development

Little is known about the precise role estrogens and progesterone might play in BBD pathophysiology. Concerning the development of FA, a controversy exists concerning the importance of hormonal effects. Some authors have found significant increases in plasma estradiol, whereas others have observed normal levels [22, 23]. It is well established that in addition to the biosynthesis of estrogen by the ovaries, some normal and tumor tissues possess enzymatic systems necessary for the local formation of estrogens [24]. Two main pathways involved in estrogen biosynthesis in breast cancer are well documented: the aromatase pathway, which transforms androgens into estrogens, and the sulfatase pathway, which converts estrogen sulfates to estrogens. Information relative to the evaluation of various estrogens, as well as the enzymes implicated in their biosynthesis in the tumoral tissues of BBD, is very limited. Pasqualini et al. [25] have shown that breast fibroadenomatous tissues contain high levels of estradiol, estrone, and their sulfates, and that these concentrations are significantly higher than in the normal area of breast tissue. The analysis of plasma estrogens showed no difference compared to healthy control women. This information extends the intracrine organ concept. How can this local production of estrogens be controlled? At present, information on this point is limited, but an interesting observation is that in BBD the production of progesterone is subnormal during the luteal phase of the menstrual cycle [26].

In this connection, it is worthwhile to note that progesterone can modify the action of estradiol in endometrial tissue by increasing the metabolism of estradiol to estrone, an effect mediated by an increase in activity of 17β-hydroxysteroid dehydrogenase [27], an enzyme which has been found in breast tissues. Estrogen receptors (ER) are present in a relatively high proportion in FA [28]. Progesterone receptors (PR) are also present in a proportion of FA [29]. Studies of the levels of ER and PR during the menstrual cycle in patients with FA show that ERs increase throughout the follicular phase, reach maximal values in the pre-ovulatory phase, and decrease during the luteal phase. PRs are high in the follicular phase [30]. These data provide additional information on the hypothesis of hormonal dependence of FA.

In addition, others have found increased expression of Bcl-2 in epithelial cells of FA [31]. This gene extends cell life by preventing the onset of apoptosis. They also showed that in normal breast, the level of Bcl-2 varied with the menstrual cycle, showing a very strong statistical link between high levels of circulating progesterone and weak Bcl-2 staining in lobules and ducts. This progesterone-dependent variation was absent in FA, where no other correlation was found, either with levels of estradiol, FSH, or LH. These results suggest an influence of progesterone on Bcl-2 expression which might be lost in FA. This finding raises the question of the involvement of altered regulation of the apoptotic process in the formation of such benign lesions.

Concerning breast pain and nodularity, two hypotheses have been raised: increased estrogen secretion from the ovary, and deficient progesterone production. As described by our group in 1979 [32], there can be a significantly depressed level of progesterone in women presenting with mastalgia and nodularity.

With respect to the development of cysts, the responsible factors are mostly unknown. There is some indirect evidence to implicate hyperestrogenism, either absolute or relative. There is also evidence that acini dilate towards the end of the menstrual cycle, and that this is an estrogen effect [17]. It has been suggested that excess unopposed estrogen in premenopausal patients maintains the acini in a dilated state, and there are also a number of cases related to estrogen therapy in post-menopausal patients. England et al. demonstrated increased mean levels of serum estradiol-17β in 13 women with cysts, although a break-down of the data shows that seven had high levels, four were normal, and two were reduced [33].

Implications of Prolactin in BBD Development

PRL and IGF-I receptors are present in about 50% of cases of FA, but there are no data concerning their potential implications in FA physiopathology.

PRL secretion has been studied in patients with cyclical mastalgia. No difference with controls has been found in basal levels (even on 24-h profiles), but two teams [34, 35] found a greater rise in PRL stimulated by TRH in patients with mastalgia than in control patients. These studies suggest a disturbance of hypothalamic control in women with cyclical mastalgia.

The cause of cyst development is not yet determined, and a hormonal basis remains unproven. Nevertheless, Gately et al. [36] have found both basal and stimulated levels of biologically active PRL raised in patients with breast cysts.

In humans, in addition to being secreted by lactotroph cells of the anterior pituitary, PRL is also produced by numerous

other cells and tissues. Ten years ago, Vonderhaar and colleagues demonstrated that PRL is synthesized by human mammary tumor cell lines, and that neutralizing anti-PRL antibodies inhibit cell proliferation [37]. These observations were the first arguments to suggest the existence of locally produced PRL stimulating cell proliferation via an autocrine–paracrine loop. We and others demonstrated that co-expression of hPRL and its receptor is also observed in normal and tumor human mammary biopsies [38–40], suggesting the physiological relevance of autocrine PRL. Since expression of the PRL receptor is increased in benign and malignant mammary tumors [39, 40], it is possible that the autocrine–paracrine loop involving local PRL plays an important role in mammary tumor growth [41–45]. Our laboratory has recently developed a new transgenic model, in which the overexpression of human PRL is restricted to the last third of gestation and lactation (transgene containing the promoter of a milk protein gene). Interestingly, sporadic overexpression of hPRL in the mammary gland leads to various dystrophic lesions, such as abnormally differentiated epithelia, squamous metaplasia, and calcified cystic lesions, as well as benign tumors such as papillomas [46]. This new animal model might be very interesting to better understand the mechanisms underlying the actions of autocrine PRL in the development of benign mammary tumors, with possible extrapolation to similar pathologies in humans, the etiologies of which still remain partially unknown [13, 47].

Implications of Growth Hormone in BBD Development

Nothing is known about the role of GH and IGFs in the development of specific BBD. Nevertheless, it has been found that the human mammary gland is also a source of growth hormone synthesis [48]. This mammary GH may have local autocrine or paracrine effects on proliferation and differentiation of mammary epithelium. Apart from direct effects on recruitment of stem cells, GH may also stimulate the local expression of IGF-I in stromal cells of the mammary fat pad. Since expression of mammary GH is associated with local expression of IGFs and their binding proteins (IGFBPs), it is thus creating a proliferative environment for the glandular epithelium. Also, treatment with GH may induce mammary gland hyperplasia, as has been shown in aging primates [49].

Many studies have been published concerning the role of insulin-like growth factors (IGFs) in breast tumor development, but little is known about their involvement in BBD or even normal breast development. Numerous data suggest that IGFBP-3 may act to decrease cell growth in normal and neoplastic tissue through complexing IGF-I, thereby reducing mitogenic signaling by the IGF-I pathway. Holdaway et al. [50] have found that there is an increase in IGFBP-3 in tissues involved in benign lesions and neoplasia, which could reflect a regulatory attempt to decrease mitogenic activity. This protective modification of serum IGFBP-3 levels in those with benign breast lesions appears to be lost in malignant breast disease, presumably allowing comparatively higher exposure of tumor tissue to unbound IGF. IGFs are potent mitogens for breast tumor epithelial cells, with a paracrine growth-promoting role. Cullen et al. [51] have shown, in primary cultures of breast fibroblasts from benign and malignant lesions, that IGF-I is expressed in fibroblasts from benign breast tissue. In contrast, IGF-II is expressed in tumor-derived fibroblasts.

Implication of Other Growth Factors in Mammary Gland Development

FGF

In addition to hormonal regulation, a complex system of locally synthesized growth factors is involved in the biological control of mammary gland cells. Little is known concerning the role of growth factors in the development of normal human breast tissue and their implication in BBD. Most studies have focused on defining localization, expression, and functions of these growth factors in tumoral breast tissue. One of the key questions is whether, when correctly regulated, the oncogenes implicated in mammary cancer are also involved in normal mammary gland development. Fantl et al. [52] have shown that two oncogenes identified in mammary cancer studies have crucial functions in the growth and differentiation of the normal mammary gland. Their results clearly demonstrate a need for signaling by fibroblast growth factors (FGFs) to produce the normal density of lobuloalveolar growth during pregnancy in mice. FGFs are pleiotropic cell to cell signaling molecules that can act as broad spectrum mitogens, promote cell migration, or modulate cellular differentiation, depending on their context. The family of FGFs includes at least 20 structurally related peptides, of which the acidic fibroblast growth factor (aFGF) is one of the best studied. aFGF is a well known stimulator of fibroblast, epithelial, and endothelial cell proliferation, and FGFR4 is a highly specific receptor for aFGF. Since aFGF and FGFR4 could be involved in the differentiation and growth of benign lesions, La Rosa et al. [11] investigated whether they had a role in modulation of the growth of fibroadenomas. Their results indicate that both aFGF and FGFR4 are expressed in epithelial cells, suggesting that these peptides could be involved in a paracrine/autocrine regulation of tumor growth or, at least, in the modulation of cell functions. In addition, FGFR4 is also strongly expressed in stromal cells, and this finding suggests a paracrine/autocrine control of stromal proliferation through interactions of aFGF. Their results suggest that aFGF and FGFR4

might be involved in the modulation of normal breast cell functions and, in addition, that they might regulate the growth of both epithelial and stromal cells of FA.

In this study, myoepithelial cells were negative for both aFGF and FGFR4, indicating that this growth factor-receptor system is not involved in the modulation of the functions of these cells. It has also been reported [53, 54] that myoepithelial cells do express bFGF, another member of the FGF family. Conversely, epithelial cells and stroma do not express bFGF. This protein has biological actions similar to those of aFGF and can bind to FGFR4, although with a lower affinity than aFGF. The close proximity of the myoepithelial cells to the basement lamina in the breast could be important for controlling epithelial cell proliferation and extracellular matrix formation during breast growth and development. This hypothetical pathway might be mediated principally by bFGF. In addition to FGFR4, it has been found that epithelial cells of normal breasts and of benign breast lesions also express FGFR1, FGFR2, and FGFR3. Taken together, these results suggest that there is a functional interaction among myoepithelial, epithelial, and stromal cells through the secretion of aFGF and bFGF, which can bind to various FGFRs. Expression of bFGF in normal mammary gland and benign mammary lesion has been investigated in several studies. Barraclough et al. [55] have suggested, based on the results obtained with the rat mammary cell lines, that the remodeling of the basement membrane during normal growth and development of the ductal tree of the mammary gland may lead to the release of sequestered bFGF, which may then act on the cells of the terminal ductal structures. They raise the hypothesis that a similar situation may exist during the local uncontrolled growth of parenchymal cells in benign breast lesions.

TGF β and α

When studying expression of bFGF in the human mammary gland, Gomm et al. [54] also studied that of TGF-β1. It was shown to be located in the periductal and intraductal stroma, closely associated with epithelial or myoepithelial cells in the benign (and malignant) breast. Normal mammary epithelial cells show a strong growth inhibition and differentiative response to TGF-β1, suggesting a developmental role for this growth factor in the normal mammary gland [56–58]. Under normal conditions, this growth factor could inhibit epithelial cell proliferation in two ways, by acting either directly on the epithelial cells themselves or indirectly by stimulating the growth of fibroblasts and collagen fibers, thus restricting the expansion of the epithelial cells. The extensive TGF-β1 staining seen in FA in their study is suggestive of the latter possibility. TGF-β1 and bFGF may be acting in concert in the breast. TGF-β1 has been shown to modulate the activity of bFGF in a variety of other tissues and to inhibit the activation of plasminogen activator and other proteases which are positively regulated by bFGF. Thus, the relative locations of TGF-β1 and bFGF seen in their studies may be significant in the development of the normal mammary gland, and changes in their synthesis, storage, or activity could upset the delicate balance of growth factor control, leading to tumor formation.

Inhibins and Activins

Inhibins and activins are members of the TGF-β superfamily. They seem to participate in the differentiation of mammary epithelial cells and in the growth and morphogenesis of primary or transformed mammary epithelial cells. Di Loreto et al. [59] have shown for the first time that inhibin and activin α and β subunits are expressed in human breast tissue. Their results suggest a local synthesis by mammary epithelial and endothelial cells.

The physiological role of these peptides in the breast remains obscure, but they might be involved in pathological cell growth, since their different subunits are differently expressed in normal mammary epithelium, fibrocystic disease, and benign and malignant breast tumors.

Role of Mesenchymal Cells

As we have previously discussed, signals for growth and differentiation of epithelia are frequently provided by neighboring mesenchymal cells. The molecular basis for signals exchanged during mesenchymal–epithelial interactions is provided by paracrine signaling systems consisting of epithelial tyrosine kinase receptors and their mesenchymal ligands. Hepatocyte Growth Factor/Scatter Factor (HGF/SF) and the c-met receptor constitute one of these paracrine signaling systems.

Concerning the expression of HGF/SF in human breast pathology, Wang et al. [60] have shown by in situ hybridization its expression both in benign and neoplastic breast epithelial cells. The most abundant expression in benign tissue appears to correspond to proliferative activity, as in the periphery of lactational acini, with little or no detectable expression by fully lactationally active cells. It is also expressed strongly in areas of adenosis, but not in normal ducts and lobules.

PDGF

Another growth factor that plays an important role in the interactions between epithelial and stromal cells, and is essential for normal breast tissue development, is platelet-derived growth factor (PDGF). Its role and that of its beta receptor (PDGFRβ) have been investigated in fibro-

epithelial breast tumors [61]. Breast tissue development and maintenance of structural relationships depend on bidirectional epithelial–stromal interactions, which are mediated by growth factors and other intercellular signals. The closely apposed epithelial and stromal elements of FA and phyllodes tumors are likely to interact.

Noguchi et al. [9] have suggested that FA are composed of polyclonal elements that can undergo somatic mutation, resulting in monoclonal proliferation and transformation to a phyllodes tumor. Also, benign phyllodes tumors may recur as higher grade lesions and can probably transform if left in situ. Epithelial hyperplasia may occur in phyllodes tumors.

In their study, Feakins et al. [61] found that phyllodes tumor epithelium usually showed PDGF/PDGFRβ co-positivity, suggesting that PDGF-mediated autocrine pathways might stimulate epithelial proliferation. Stromal growth factors, however, could also be responsible. These results suggest that PDGF influences the pathogenesis of fibro-epithelial breast tumors, and that PDGF-dependent paracrine and autocrine mechanisms may operate.

Conclusions

It is clear that there is a paucity of information concerning the mechanisms leading to the onset of BBD. One of the reasons is undoubtedly that in the past the focus of most clinical and research teams has been on breast cancer, and not all patients presenting with BBD have a greater risk to develop breast cancer. However, further clinical studies will be necessary to determine the mechanisms regulating such disorders, to better understand the involvement of hormones and growth factors in BBD, and finally to better define different therapeutic approaches.

References

1. Sitruk-Ware R, Plu-Bureau G. Epidemiology and treatment of benign breast disease: effect of progestins on breast disease. In: Sitruk-Ware R, Mishelle DR Jr., Editors. Progestins and antiprogestins in clinical practice. New-York: Marcel Dekker; 2000. pp. 327–40.
2. Dupont WD, Page DL. Risk factors for breast cancer in women with proliferative breast disease. N Engl J Med 1985;312:146–51.
3. Hughes LE, Mansel RE, Webster DJT. Aberrations of normal development and involution (ANDI): a new perspective on pathogenesis and nomenclature of benign breast disorders. Lancet 1987;2:1316–9.
4. Plu-Bureau G, Thalabard JC, Sitruk-Ware R, Asselain B, Mauvais-Jarvis P. Cyclical mastalgia as a marker of breast cancer susceptibility: results of a case-control study among French women. Br J Cancer 1992;65:945–9.
5. Goodwin PJ, DeBoer G, Clark RM, Catton P, Redwood S, Hood N, Boyd NF. Cyclical mastopathy and premenopausal breast cancer risk. Results of a case-control study. Breast Cancer Res Treat 1995;33:63–73.
6. Goehring C, Morabia A. Epidemiology of benign breast disease, with special attention to histologic types. Epidemiol Rev 1997;19:310–27.
7. Hughes LE, Mansel RE, Webster DJT. Benign disorders and diseases of the breast—concepts and clinical management. 2nd ed. W.B. Saunders; 2000. Chap. 2, pp. 7–20.
8. Parks AG. The microanatomy of the breast. Ann R Coll Surg Engl 1959;25:295–311.
9. Noguchi S, Yokouchi H, Aihara T, Motomura K, Inaji H, Imaoka S, Koyama H. Progression of fibroadenoma to phyllodes tumor demonstrated by clonal analysis. Cancer 1995;76:1779–85.
10. Hughes LE, Mansel RE, Webster DJT. Benign disorders and diseases of the breast—concepts and clinical management. 2nd ed. W.B. Saunders; 2000. Chap. 3, pp. 21–34.
11. La Rosa S, Sessa F, Colombo L, Tibiletti MG, Furlan D, Capella C. Expression of acidic fibroblast growth factor (aFGF) and fibroblast growth factor receptor 4 (FGFR4) in breast fibroadenomas. J Clin Pathol 2001;54:37–41.
12. Dupont WD, Page DL, Parl FF, Vnencak-Jones CL, Plummer WD Jr, Rados MS, Schuyler PA. Long term risk of breast cancer in women with fibroadenoma. New Engl J Med 1994;331:10–15.
13. Hughes LE, Mansel RE, Webster DJT. Benign disorders and diseases of the breast—concepts and clinical management. 2nd ed. W.B. Saunders; 2000. Chap. 7, pp. 73–94.
14. Cole-Beuglet C, Soriano RZ, Kurtz AB, Goldberg BB. Fibroadenoma of the breast. Sonomammography correlated with pathology in 122 patients. American Journal of Radiology 1983;140:369–75.
15. Mauvais-Jarvis P. Le traitement hormonal des mastopathies bénignes. Bull Cancer 1991;78:365–71.
16. Kumar S, Mansel RE, Hughes LE, Edwards CA, Scanlon MF. Prediction of response to endocrine therapy in pronounced cyclical mastalgia, using dynamic tests of prolactin release. Clin Endocrinol 1985;23:699–704.
17. Hughes LE, Mansel RE, Webster DJT. Benign disorders and diseases of the breast—concepts and clinical management. 2nd ed. W.B. Saunders; 2000. Chap. 9, pp. 123–35.
18. Hughes LE, Mansel RE, Webster DJT. Benign disorders and diseases of the breast—concepts and clinical management. 2nd ed. W.B. Saunders; 2000. Chap. 6, pp. 61–72.
19. Cowen PN, Benson EA. Cytological study of fluid from benign breast cysts. Br J Surg 1979;66:209–11.
20. Angeli A, Bradlow HL, Chasalon FI, Dogliotti L. Biochemistry of breast cyst fluid. Ann N Y Acad Sci 1990;586:1–296.
21. Hughes LE, Mansel RE, Webster DJT. Benign disorders and diseases of the breast—concepts and clinical management. W.B. Saunders, 2d ed., 2000; chap. 4, pp 35–47.
22. De Boever J, Vandekerckhove D. Benign breast disease: steroid concentrations. J Steroid Biochem 1982;Abst 338.
23. Wang DY, Fentiman IS. Epidemiology and endocrinology of benign breast disease. Breast Cancer Res Treat 1985;6:5–39.
24. Pasqualini JR, Chetrite G. Activity and regulation of sulfatase, sulfotransferase and 17β-hydroxysteroid dehydrogenase in breast cancer. In: Pasqualini JR, Katzenellenbogen BS, Editors. Hormone-dependent cancer. New York: Marcel Dekker; 1996. pp. 21–80.
25. Pasqualini JR, Cortes-Prieto J, Chetrite G, Talbi M, Ruiz A. Concentrations of estrone, estradiol and their sulfates, and evaluation of sulfatase and aromatase activities in patients with breast fibroadenoma. Int J Cancer 1997;70:639–43.
26. Martin PM, Kuttenn F, Serment H, Mauvais-Jarvis P. Studies on clinical, hormonal and pathological correlations in breast fibroadenomas. J Steroid Biochem 1978;9:1251–55.
27. Tseng L, Gusberg SB, Gurpide E. Estradiol receptor and 17β-hydroxysteroid dehydrogenase in normal and abnormal human endometrium. Ann N Y Acad Sci 1977;286:190–8.

28. Allegra JC, Lippman ME, Green L, Barlock A, Simon R, Thompson EB, Huff KK, Griffin W. Estrogen receptor values in patients with benign breast disease. Cancer 1979;44:228–31.
29. Martin PM, Kuttenn F, Serment H, Mauvais-Jarvis P. Progesterone receptors in breast fibroadenomas. J Steroid Bioch 1979;11:1295–98.
30. Kuttenn F, Fournier S, Durand JC, Mauvais-Jarvis P. Estradiol and progesterone receptors in human breast fibroadenomas. J Clin Endocrinol Metab 1981;52:1225–9.
31. Ferrieres C, Cuny M, Simony-Fontaine J. Variation of Bcl-2 expression in breast ducts and lobules in relation to plasma progesterone levels: overexpression and absence of variation in fibroadenomas. J Pathol 1997;183:204–11.
32. Mauvais-Jarvis P, Sitruk-Ware R, Kuttenn F, Sterkers N. Luteal phase insufficiency: a common pathophysiologic factor in development of benign and malignant breast diseases. Comment Res Breast Dis 1979;1:25–59.
33. England PC, Skinner LG, Cottrell KM, Sellwood RA. Sex hormones in breast disease. Br J Surg 1975;62:806–9.
34. Peters F, Pickardt CR, Zimmerman G, Breckwoldt M. PRL, TSH and thyroid hormones in benign breast disease. Klin Wochenschr 1981;59:403–7.
35. Kumar S, Mansel RE, Hughes LE, Woodhead JS, Edwards CA, Scanlon MF, Newcombe RG. Prolactin response to thyrotropin-releasing hormone stimulation and dopaminergic inhibition in benign breast disease. Cancer 1984;53:1311–5.
36. Gately CA, Maddox PR, Jones DL. Biologically active prolactin in patients with macroscopic breast cysts. Br J Surg 1992;79:1238.
37. Ginsburg E, Vonderhaar BK. Prolactin synthesis and secretion by human breast cancer cells. Cancer Res 1995;55:2591–5.
38. Clevenger CV, Chang WP, Ngo W, Pasha TM, Montone KT, Tomaszewski JE. Expression of prolactin and prolactin receptor in human breast carcinoma. Am J Pathol 1995;146:695–705.
39. Reynolds C, Montone KT, Powell CM, Tomaszewski JE, Clevenger CV. Expression of prolactin and its receptor in human breast carcinoma. Endocrinology 1997;138:5555–60.
40. Touraine P, Martini JF, Zafrani B, Durand JC, Labaille F, Malet C, Nicolas A, Trivin C, Postel-Vinay MC, Kuttenn F, Kelly PA. Increased expression of prolactin receptor gene assessed by quantitative polymerase chain reaction in human breast tumors versus normal breast tissues. J Clin Endocrinol Metab 1998;83: 667–74.
41. Clevenger CV, Plank TL. Prolactin as an autocrine/paracrine factor in breast cancer. J Mammary Gland Biol Neopl 1997;2:59–68.
42. Vonderhaar BK. Prolactin: the forgotten hormone of human breast cancer. Pharmacol Ther 1998;79:169–78.
43. Goffin V, Touraine P, Pichard C, Bernichtein S, Kelly PA. Should prolactin be reconsidered as a therapeutic target in human breast cancer? Mol Cell Endocrinol 1999;151:79–87.
44. Llovera M, Touraine P, Kelly PA, Goffin V. Involvement of prolactin in breast cancer: redefining the molecular targets. Exp Gerontol 2000;35:41–51.
45. Clevenger CV, Furth PA, Hankinson SE, Schuler LA. The role of prolactin in mammary carcinoma. Endocr Rev 2003;24:1–27.
46. Manhes C, Kayser C, Bertheau P, Kelder B, Kopchick JJ, Kelly PA, Touraine P, Goffin V. Local over-expression of prolactin in differentiating mouse mammary gland induces functional defects and benign lesions, but not carcinoma. J Endocrinol 2006;190:273-87.
47. Ryska A, Reynolds C, Keeney GL. Benign tumors of the breast with multinucleated stromal giant cells. Immunohistochemical analysis of six cases and review of the literature. Virchows Arch 2001;439:768–75.
48. Mol JA, Henzen-Longmans SC, Hageman Ph, Misdorp W, Blankenstein MR, Rijnberk A. Expression of the gene encoding GH in the human mammary gland. J Clin Endocrinol Metab 1995; 80:3094–6.
49. Ng ST, Zhou J, Adesanya OO, Wang J, LeRoith D, Bondy CA. Growth hormone treatment induces mammary gland hyperplasia in aging primates. Nature Medicine 1997;10:1141–4.
50. Holdaway IM, Mason BH, Lethaby AE, Singh V, Harman JE, MacCormick M, Civil ID. Serum levels of insulin-like growth factor binding protein-3 in benign and malignant breast disease. Aust NZ J Surg 1999;69:495–500.
51. Cullen KJ, Smith HS, Hill S, Rosen N, Lippman ME. Growth factor messenger RNA expression by human breast fibroblasts, benign and malignant lesions. Cancer Res 1991;51:4978–85.
52. Fantl V, Creer A, Dillon C, Bresnick J, Jackson D, Edwards P, Rosewell I, Dickson C. Fibroblast growth factor signaling and cyclin D1 function are necessary for normal mammary gland development during pregnancy. Advances in Experimental Medicine and Biology, vol. 480 "Biology of the mammary gland" 2000. Chap 1, pp. 1–7.
53. Coombes RC, Gomm JJ, Luqmani YA. Acidic and basic FGF and their receptors in normal and malignant breast cells. Endocrinology 1994;35:259.
54. Gomm JJ, Smith J, Ryall GK, Baillie R, Turnbull L, Coombes RC. Localization of basic fibroblast growth factor and transforming growth factor β1 in the human mammary gland. Cancer Res 1991;51:4685–92.
55. Barraclough R, Fernig DG, Rudland PS, Smith JA. Synthesis of basic fibroblast growth factor upon differentiation of rat mammary epithelial to myoepithelial-like cells in culture. J Cell Physiol 1990;144:333–44.
56. Ethier SP, Van de Velde. Secretion of TGF-β like growth inhibitor by normal rat mammary epithelial cells. J Cell Physiol 1990;142:15–20.
57. Lippman ME, Dickson RB. Growth control of normal and malignant breast epithelium. Proc R Soc Edinburgh 1989;95b: 89–106.
58. Baillie R, Coombes RC, Smith J. Multiple forms of TGF-β1 in breast tissues: a biologically active form of the small latent complex of TGF-β1. European Journal of Cancer 1996;32A(9):1566–73.
59. Di Loreto C, Reis FM, Cataldi P, Zuiani C, Luisi S, Beltrami CA, Petraglia F. Human mammary gland and breast carcinoma contain immunoreactive inhibin/activins subunits: evidence for a secretion into cystic fluid. Eur J Endocrinol 1999;141:190–4.
60. Wang Y, Selden C, Morgan N, Stamp GWH, Hodgson HJF. Hepatocyte growth factor/scatter factor expression in human mammary epithelium. Am J Pathol 1994;144:675–82.
61. Feakins RM, Wells CA, Young KA, Sheaff MT. Platelet-derived growth factor expression in phyllodes tumors and fibroadenomas of the breast. Hum Pathol 2000;31:1214–22.