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Review

Epidemiology and endocrinology of benign breast disease

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I Introduction

In 1845, Astley Cooper [37] reported in his monograph 'The Anatomy and Diseases of the Breast' the co-existence of benign cysts and scirrhous carcinoma. Since this first description of joint presence of benign and malignant disease, a large literature has accumulated attempting to define and quantify the link between benign disease and cancer. Unfortunately, the issue has been clouded rather than clarified because of the absence of an agreed clinical and pathological terminology, inadequate duration of follow-up, or the absence of an appropriate control population.

We have attempted to identify which benign breast lesions carry a pre-malignant potential. We have analysed the role of the endocrine system in the genesis of such lesions, and have indicated areas of potential interest for future work. An improved understanding of the etiology of pre-malignant breast disease might allow the formulation of strategies for the prevention of breast cancer in certain susceptible individuals.

II Classification

The term 'benign breast disease' in itself can lead to confusion since it maybe taken to imply a specific single disease whereas it embraces a wide variety of conditions. An accurate dissection into homogenous components is complicated by a lack of agreement among clinicians and pathologists concerning terminology.

(a) Clinical confusion

Some clinicians include all patients with breast symptoms within the category of benign breast disease (BBD). Defined in this way, the term would include almost all the female population since most women suffer from some degree of pre-menstrual breast pain during their reproductive years. At varying levels of severity, or when such pain becomes non-cyclical, affected women may present at breast clinics and then are labelled as suffering from mastalgia or mastodynia. Many studies of BBD have included such patients, but there is no evidence that these women have a distinct disease entity, nor are they suffering from a pre-malignant breast condition. Indeed, a histological study of biopsies from patients with and without mastalgia was unable to demonstrate any specific change in the breasts of women suffering from breast pain [206].

(b) Pathological confusion

In 1905, J Collins Warren [205] wrote 'As an instance of the confusion in nomenclature, I might here state that in 199 cases of benign disease of the

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breast occurring in the Massachusetts General Hospital in ten years, 70 different pathological diagnoses appeared on the record books'. In the ensuing three quarters of a century, an even worse clutter of eponymous and descriptive terminology has accumulated [see 5, 13, 17, 32, 37, 42, 95, 99, 167, 168, 173, 205]. Foote and Stewart [57] proposed a greatly simplified system, with well defined histological terms, which now forms the foundation of pathological reporting of benign biopsy specimens. It is important to be aware, as they indicated, that several different histological lesions may co-exist within an individual biopsy specimen, and indeed on a single histological section. It is an unfortunate fact of life that histological reporting involves an important subjective element, so that different pathologists may be unable to agree on a diagnosis for some specimens. However, the universal adoption of a common nomenclature would at least facilitate the possibility of comparative studies between different centres. This non-uniformity also makes for difficulties when reviewing the literature, particularly because pathological descriptions are not always available, and for this reason we have used the terms quoted by the various authors.

III Benign disease and breast cancer risk

(a) Follow up of proven gross cystic disease

There are two major clinical categories of BBD comprising either cysts treated by aspiration, or solid lesions treated by excision or incision biopsy. The majority of simple cysts are managed by aspiration, which is of great advantage to both patient and surgeon because of the simplicity of the treatment. The disadvantage is that no histological information is available concerning the underlying pathological process responsible for cyst formation. This group of patients may therefore contain patients in which cyst formation results from epithelial hyperplasia and others in which cell proliferation is absent. Haagensen [73] has carefully followed 1693 patients with proven gross cystic disease, of whom 72 subsequently developed breast cancer compared with an expected rate of 17.4 among the New York population (a relative risk of 4). Apart from the previously mentioned heterogeneity of the study group, there may be an additional disadvantage in comparing a group of hospital patients with the non-hospital population. Patients presenting to clinics with breast related problems form a selected group in which ethnic factors and family history of breast cancer may mean that they already carry an increased risk of breast cancer with or without the presence of palpable breast pathology.

(b) Follow-up of biopsied BBD

There have been several reported prospective studies of patients with biopsied benign breast lesions to determine the incidence of subsequent cancer compared with control populations. The study with the longest follow-up is that of Monson et al. [131], in which a relative risk of 2.5 was found among women with BBD followed for at least 30 years after biopsy. Table 1 shows the results of those follow-up studies in which the median follow-up time was greater than 5 years. An almost invariable increase in risk was seen except in two of the shorter-term follow-up series. Taken overall, an approximate risk ratio of 3 was obtained. Against this, Devitt has raised a note of dissent. He originally argued that since only 7% of his breast cancer patients had had a previous biopsy for BBD, that there was a chance association between the two conditions [43]. In a further paper describing a greater number of patients [44], he found that 11% of cancer patients had previous biopsies for BBD, and that these patients were 20 years older than the peak age for BBD. His arguments ignore two factors, firstly that he had not considered the biopsy rate in the population from which his patients were derived, and secondly the considerable delay that might occur between benign biopsy and presentation with malignancy.

Considering a hypothetical cohort of 1000 women, the likely benign biopsy rate is 10%. Of the entire population followed to death, approximately 60 (6%) will develop breast cancer. If there were no increased risk carried by benign breast

biopsy, these 60 patients would be proportionately distributed between the biopsied and non-biopsied groups in a ratio of 6 to 54. Taking Devitt's figures, if 11% (11) of the BBD group develop cancer, then there will be 49 in the non-biopsied group. These cancer rates of 5.4% and 11% give an approximate risk ratio of 2 for the BBD group, which is consistent with the published figures.

However, although BBD may carry an increased risk, these patients still form the minority of breast cancer cases and thus would not be useful as a basis for screening. A more helpful approach would be to determine which patients with BBD have an increased risk of breast cancer and study them to determine whether they carry any endocrine or biochemical stigmata, and then to look for these abnormalities in the general population.

(c) Which types of BBD carry the risk?

Using a combination of subgross and histological examination, Wellings et al (207) studied mastectomy specimens, contralateral breasts removed prophylactically, and post-mortem material derived from patients dying of diseases other than breast cancer. They demonstrated that the terminal ductal-lobular unit (TDLU) was the anatomical origin of the majority of breast lesions. A spectrum of abnormalities was found, ranging from lobular hyperplasia followed by in situ ductal carcinoma. The unfolding of the TDLU by expansion of tumour produced the apparent ductal origins of carcinomata.

Page et al [147] have reviewed the pathological material from 1127 patients who had BBD biopsies, of which 94% were followed up for a minimum of 15 years. They found that the increased risk of breast cancer was carried only by the patients in whom epithelial proliferation was found. The presence of atypical lobular hyperplasia conveyed a sixfold risk for those under 45 and a threefold risk for those over 45. Ductal hyperplasia conveyed no risk for patients under 45 at time of biopsy but doubled the risk in those aged more than 45, as did the presence of papillary apocrine change and apocrine-like hyperplasia. Unlike Black et al [16] and Kodlin et al [94], they did not find any increased risk for atypical ductal lesions compared with hyperplastic ductal lesions without atypia, in a complementary study, followed up for an average of almost 13 years. In addition to histological review, clinical information on age, parity, period regularity, mastodynia, estrogen use, and nipple discharge was available.

Relative risks were calculated from US population incidence rates and the incidence rate in the local population. For the biopsied population the relative risk was 2.1. This risk was not affected by age at biopsy, but was doubled for bilateral breast lesions, and increased with the size of the original biopsied lesion.

Separation into histological subtypes showed no

Table 1. Follow-up of benign breast biopsies.

Number	Follow-up (yrs)		Cancers	% Cancers	Risk	Investigator & date [Reference]
	Mean	Median				
290	6.1	8	2	0.69	±	Campbell 1934 [31]
183		5.5	6	3.3	5	Clagett et al 1940 [33]
484		12	4	0.8	±	Hendrick 1957 [78]
466	9.1	14.5	10	2.1		Hodge et al 1959 [82]
284	13		7	2.5	1.73	Davis et al 1964 [39]
1051	8.75	13	25	2.4	1.6	Veronesi & Pizzocaro 1968 [196]
110		18	10	9.1	4.8	Potter et al 1968 [154]
733	30.3		49	6.7	2.5	Monson et al 1976 [131]
2900	6.9		64	2.2	2.7	Kodlin et al 1977 [94]
747		17	9	0.93	4.7	Coombs et al 1979 [36]

increase in risk for fibroadenomata or inflammatory lesions. The increased relative risk was carried by patients with epithelial hyperplasia or papillomatosis, and further increased by the presence of microcalcification. No increased risk was demonstrated for intraductal papilloma, unlike the studies of Donnelly et al [46], Kilgore et al [93], Moore et al [133], and Buhl-Jorgensen et al [28].

Dupont and Page have recently produced further evidence concerning the low risk of the majority of patients who have had a benign biopsy [213]. The presence of epithelial hyperplasia carried a two-fold risk, compared with those without proliferative lesions. This risk increased to five-fold when atypical hyperplasia was present and to eleven-fold among those with a family history of breast cancer together with atypical lobular hyperplasia. However, this last high-risk group comprised only 39 out of 10,366 women.

Thus epithelial hyperplasia clearly emerges as a lesion with pre-malignant potential. Two points should be made. Firstly, epithelial hyperplasia rarely produces a palpable lump. The discovery of hyperplasia will depend upon a biopsy being performed because of some other lesion, either a cyst or a fibroadenoma, which alerts the patient or physician to breast pathology. Secondly, many patients with epithelial hyperplasia will never develop breast cancer. This implies that for many patients the epithelial cells are not committed to malignant differentiation or de-differentiation. Malignant progression may depend upon hormonal promotion, and thus the demonstration of an endocrine abnormality might delineate those patients most at risk of developing breast cancer, both in those with known epithelial hyperplasia and also among those with latent disease in the general population.

IV Risk factors and BBD

Factors which might be related to the risk of developing BBD, such as age or reproductive history, have been examined using both population and case-control studies. As can be seen from Table 2 none of these investigations have the same design, so that there are variations in, for example, the definition of BBD, or in matching criteria in case-control studies.

(a) Age

There have been several population-based studies on the incidence of BBD with age. Figure 1 shows the results of these investigations. All show a remarkable agreement, especially if one considers that these populations come from countries as far apart as Finland, America, Australia, and Britain. All show a peak incidence around 40 years of age. In the American study of Cole et al [35] there was a biphasic incidence curve, which was also observed by Hislop and Elwood [81] in their cohort study. This biphasic distribution reflects the difference in incidence of fibroadenoma and chronic cystic disease. The data for these two groups of disease are presented in Figures 2 and 3.

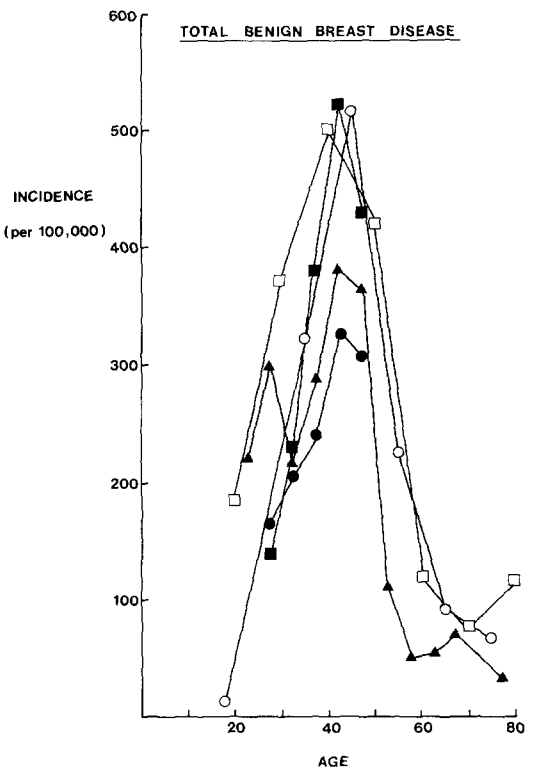

Fig. 1. Incidence of total benign breast disease with age. Data taken from Ory et al [145] (■–■), Cole et al [35] (▲–▲) Brinton et al [24] (●–●), Soini et al [182] (○–○), and Fleming et al [56] (□–□).

Table 2. Details of epidemiological studies on benign breast disease (BBD).

Investigator & date [Reference]	Category (number)	Type of experiment	Source of controls	Matching criteria	Country & racial composition	Age studied	Oral contraceptive use
Vessey et al 1972 [197]	BBD * (255)	Case-control (1:1)	Hospital	Age Ever-married Parity Date of H.A.	U.K. Controls & cases 'comparable country of birth'	16–39	66.7% never-user
Kelsey et al 1974 [92]	Cystic hyperplasia (209) Fibroadenoma (123) Mixed (32) Others (20)	Case-control (1:1)	Hospital	Age Ever-married, race Education, Date of H.A.	U.S. 331 white 53 black	20–44	159 never-user
Fasal & Paffenbarger 1975 [52]	BBD (446)	Case-control (1:2)	Hospital	Religion Race, Age, Hospital Date of H.A.	U.S. 403 white 43 black	15–50	256 never-user
Nomura et al 1977 [138]	Cystic disease (275) Fibroadenoma (45)	Case-control (1:1)	Local population	Age	U.S. white only	20–49	–
Cole et al 1978 [35]	Fibrocystic disease (642) Fibroadenoma (229) Mixed (67)	Case-control (1:2)	Local population	Age	U.S.	15–70+ (16 under 20 excluded)	–
Sartwell et al 1978 [165]	Cystic disease (783) Fibroadenoma (155) Other (94)	Case-control (1:1)	Hospital	Age Race, Ever-married, Date of H.A. Hospital Pay Status	U.S.	15–74	–
Ravnihar et al 1979 [156]	Cystic disease (318) Fibroadenoma (109) Other (70) Non-biopsied mastopathy (387)	Case-control (1:1)	Hospital	Age Date of H.A.	Yugoslavia	15–64	339 never-users
Hislop & Elwood 1981 [81]	BBD (107) Non-biopsied BBD (215)	Cohort (726 women)	–	–	Canada 'relatively homogenous'	18–38 followed for 30 yrs	339 never-users
Soini et al 1981 [182]	Benign mammary dysplasia (265) Benign tumours (23) Mixed (134)	Case-control (1:1)	Local population	Age	Finland	15–70+	–
Fleming et al 1982 [56]	Benign mammary dysplasia (808) Fibroadenoma (274) Others (188)	Population	–	–	Australia Hetero-geneous	15–75+	–

BBD = benign breast disease; H.A. = hospital admission. * Unless otherwise stated all categories are confirmed by biopsy.

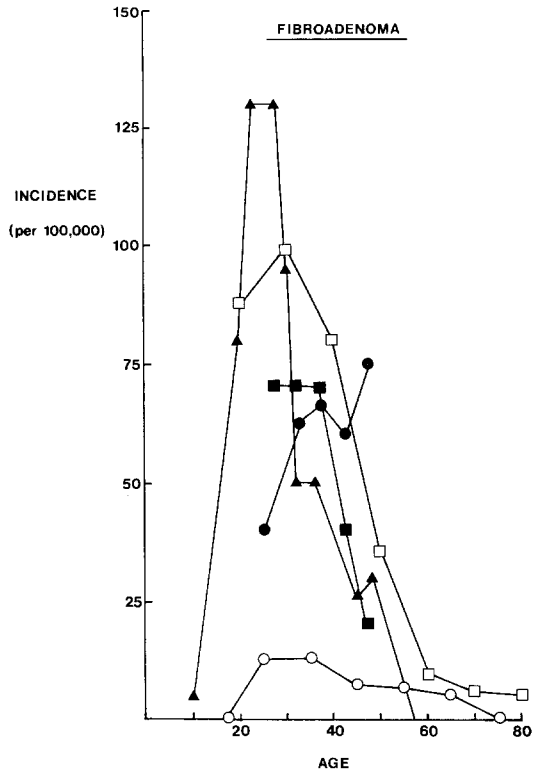

Fig. 2. Incidence of fibroadenoma with age. Key same as Figure 1.

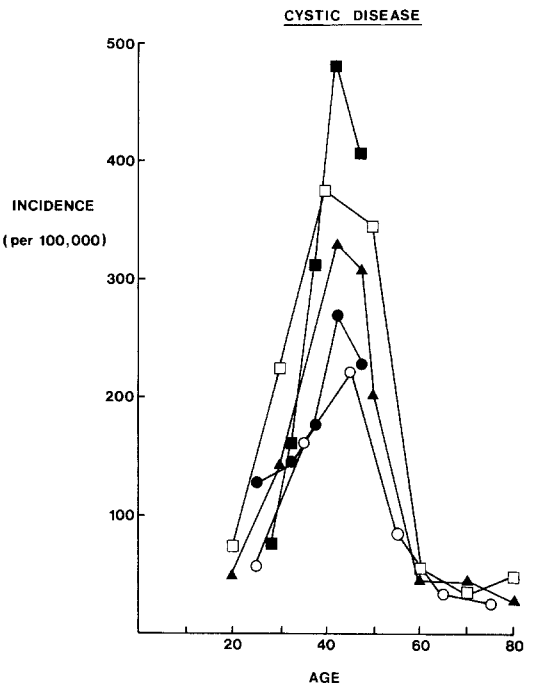

Fig. 3. Incidence of cystic disease with age. Key same as Figure 1.

That the peak incidence of fibroadenoma occurs earlier than that of cystic disease has been shown by most studies except that of Brinton et al [24]. This latter investigation was based on a selected population of women, aged 25–39, attending Family Planning Clinics. Of this group, 56% were taking oral contraceptives. The Finnish study [182] divided women into those with fibroadenomas alone and those in whom this condition was present together with cystic disease. Those in the former category show an early peak of incidence, although the level is much lower than that found in the other studies. The incidence of fibroadenoma in all patients, irrespective of whether it is accompanied by cystic disease or not, is similar to that found by Cole et al [35] and Fleming et al [56] for fibroadenoma alone, although the peak incidence occurs at a later age of 45 years.

The incidence patterns of chronic cystic disease or mammary dysplasia are remarkably similar in all studies, with a peak incidence at 40–50 years.

These findings imply that the proportion of women with fibroadenoma to chronic cystic disease will alter with age. This is borne out by the distribution of cystic disease and fibroadenoma with age, and these data are shown in Table 3.

Several studies have been performed on postmortem material. Frantz et al [63] examined breast tissue from 225 subjects, without a history of malignant or BBD, and found gross cystic disease in about 20% of subjects aged 20–39 and 35% aged 40–49. The percentage dropped to 15% in the 50–79 year age group. The major proportion (67%) of fibroadenoma was found in the age range 40–59 years. Kramer and Rush [98] studied tissue from 140 breasts of 70 women aged 70 or older and found that cysts, generally small, were present in 89% of subjects whilst intraductal hyperplasia was found in 69%.

(b) Reproductive factors

The relationship between BBD risk and reproductive factors is shown in Table 4. It is clear that there is no unanimity concerning the effect of any one factor on subsequent risk. Part of the reason for

this discordancy may be differences in the design of the studies. For example, in some investigations the controls were population-derived whilst in others they were matched hospital patients. In the study of Vessey et al [197], the controls were matched for parity and this automatically excluded any analysis of the effect of parity on risk.

However, even allowing for these considerations, a certain consensus emerges. In most studies nulliparity is associated with an increased risk of BBD (Table 4). Although Sartwell and colleagues [166] found a non-significantly increased risk among nulliparous women, the level of significance had been understated since the controls had been matched for marital status. Cole et al [35] found that there was a decreased risk of cystic disease in older nulliparous women, although in younger women this was reversed, with an increased risk of both fibroadenoma and cystic disease. The notion that women with BBD are more likely to be nulliparous is in keeping with the report of Fleming et al [56] that women with benign mammary dysplasia or fibroadenoma are less likely to have married than unaffected women.

Multiparity is associated with a decreased risk of cystic breast disease. Both Nomura et al [138] and Kelsey et al [92] report that the protective effect of multiparity extends to cystic disease but not fibroadenoma. The data of Sartwell et al [166] are also in accord with this since patients with cystic disease had fewer pregnancies compared with controls and this difference was highly significant ($P<0.001$); a similar finding was seen for fibroadenoma although the difference just reached formal significance ($P<0.05$). Since the peak incidence of fibroadenoma occurs in women aged 20–30 years, it is likely that only a few women would have achieved a high degree of multiparity and a protective effect would be difficult to detect.

Although the age at which a women has her first child is highly related to subsequent risk of breast cancer, it is clear that there is no such relationship with BBD. Most investigators have found no effect, although a few have found an increased risk of cystic disease with late age of first child. In the study of Brinton et al [24] increased risk was not statistically significant, and in the report of Nomura et al [138] it became insignificant when adjusted for other factors.

Whether a woman lactates or not probably has no effect on BBD risk. Some have found no difference, whilst Cole et al [35] and Soini et al [182] found an increased risk which was not significant in the first study and only significant in that of Soini et al [182] for a subset of patients with mammary dysplasia. It has also been stated that women who themselves had been breast-fed did not have an increased risk of BBD [134].

Although it is clear from Table 4 that the age at which menarche occurs has no effect on subsequent

Table 3. Distribution of fibroadenoma and cystic disease with age.

Cystic disease (%)		Fibroadenoma (%)		Reference
≤34 yrs	>34 yrs	≤34 yrs	>34 yrs	
51%	49%	81%	19%	[92]
26*	74	71	29	[138]
26	74	76	24	[35]
15	85	–	–	[148]
26	74	71	29	[165]
24	76	83	17	[142]
43	57	46	54	[24]
31	69	52	48	[182]
30 ± 4	70 ± 4	69 ± 5	31 ± 5	

Mean ± S.E.M.

* Population age ranged from 20 to 49 years.

Table 4. Reproductive factors and their relationship to benign breast disease (BBD).

Investigator & date [Reference]	Nulliparity	Multiparity	Late age at first child	Lactation	Age at menarche	Age at menopause
Vessey et al 1972 [197]	–	–	BBD older	–	–	–
Kelsey et al 1974 [174]	CD (P = 0.04) and FA (P = 0.06) have increased risk	Number of children CD 1.73 Controls 2.03 P<.02 FA 1.2 Controls 1.38 NS	No effect	No effect	No effect	
Fasal & Paffenbarger 1975 [52]	No effect	Number of children BBD = 2.8 Controls = 3.3 N.S.	No effect	–	No effect	9% BBD 19.4% controls menopausal
Nomura et al 1977 [138]	Number of children RR-CD 4+ 1.0 2,3 3.3 0,1 4.3	RR-FA 1.0 1.0 1.0	No effect	–	No effect	No effect
Cole et al 1978 [35]	RR Younger women: CD = 2.2 FA = 3.2 Older women: CD = 0.5 FA = 0.3 (N.S.)	Trend in CD but N.S.	Trend of increased for CD (N.S.) No risk effect for FA	Increased, but NS, risk for CD and FA	RR FA = 1.7 CD = No effect	Age RR <49 1.0 49–51 1.4 52+ 3.0 for CD
Sartwell et al 1978 [165]	RR CD = 1.1 (NS) FA = 1.6 (NS)	Fewer pregnancies in CD (P<0.001) and FA (P<0.05)	>25 years CD = 1.7 RR FA = 2.1 N.S.	–	No effect	Less natural or artificial menopause in CD
Ravnihar et al 1979 [156]	Ever pregnant CD = 90.1% P<0.05 Controls = 82.9% FA = 77.9% N.S. Controls = 72.6%	Mean no. live births CD = 1.9 Controls = 1.9 N.S. FA = 1.6 Controls = 2.0 N.S.	No effect	–	No effect	P<0.05 % Postmenopausal CD = 6.5% Controls = 11% N.S. FA = 2% Controls = 5.3% N.S.
Brinton et al 1981 [24]	–	No effect	Trends for increased risk in CD but N.S.	–	–	–
Soini et al 1981 [182]	RR CD = 1.3 (N.S.) FA = 1.1 (N.S.)	No effect	No effect	No effect except for a subset of CD	No effect	No effect
Hislop & Elwood 1981 [8]	Increased risk in women who had had abortions	Reduced risk but N.S.	No effect	No effect	–	–

BBD = benign breast disease; CD = chronic cystic disease; FA = fibroadenoma; N.S. = non-significant; RR = relative risk.

risk of BBD, age at menopause could influence risk. Several authors have shown that women with BBD are more likely to be premenopausal than age-matched controls. In the study of Sartwell et al [166] women with cystic disease were less likely to have had a natural or artificial menopause. Cole et al [35] report that an increased risk occurred in women with a higher age at menopause; women who had a natural menopause after the age of 52 had three times the risk of those in which this occurred before the age of 49.

Menstrual cycle length has been studied in women with BBD by Olsson and colleagues [141]. They found that short cycles (<21 days) occurred in 8% of patients compared to 4% of controls whilst long cycles (> 30 days) were less common (20%) than in controls (28%). There were significantly more irregular cycles in women with BBD (20%) than controls (8%). This irregularity of cycle length is in keeping with the finding that such women have a high incidence of anovulatory cycles [121].

(c) Family history of breast cancer

Morgan et al [134] in a retrospective cohort study found an increased risk of BBD in women whose mothers had breast cancer. In addition there was an enhanced, but insignificant, risk in daughters of patients with BBD. Hislop and Elwood [81] in their cohort study found that women with a sister (but not mother) with breast cancer had an increased risk of BBD, which only became significant in women aged 30 years or older.

These authors also claim that women with either a mother or sister with BBD also have an increased risk of BBD. In the case-control study of Ravnihar et al, [156] 1.5% of women with cystic disease had mothers with breast cancer compared with 0.8% in controls. The corresponding figures for fibroadenoma were 3.2% and 0.0%. However, in neither case were the differences significant. Nomura et al [138] also found that there were more women with mothers who had breast cancer in the cystic disease group than in controls, although again the difference could have been due to chance. However, as both Ravnihar et al [156] and Ernster [51] point out, these differences may be due to a heightened awareness of breast disease by the patient and the probability that surgeons would be more inclined to biopsy lesions in women with a family history.

Fasal & Paffenbarger [52] and Kelsey et al [92] were unable to detect any relationship between family history of breast cancer and subsequent risk of BBD.

(d) Obesity

There is general agreement that the incidence of biopsied BBD is inversely proportional to obesity. The cohort study of Hislop and Elwood [81] found that obesity, as measured by Quetelet's index (weight/heigth^2), was associated with a decreased risk in women aged 30 or older. There was also a correlation between breast size and risk, which was independent of obesity. The association between reduced risk and obesity was stronger after the age of 30 whilst breast size was more related to disease diagnosed before the age of 30.

Five other studies have found that patients with BBD tend to be lighter than controls although no association was found with height [24, 35, 52, 156, 182]. Brinton et al [24] found that women who were >65 kg had a 40% reduction in the incidence of fibroadenoma, cystic disease, and non-biopsied BBD as compared with lighter women weighing <55 kg. This effect was independent of oral contraceptive use and socio-economic status.

There is a significant relationship between obesity and breast size [166], and it has been suggested that a contributory factor as to why obese women have less BBD is the difficulty of detecting breast lesions.

(e) Socio-economic status

Socio-economic status appears to be a strong indicator of risk of BBD, the highest risk being in the wealthiest women. Nomura et al [138] found that cases (whether cystic disease or fibroadenoma) were better educated and had higher family incomes. Using mean rental value of housing as an index of socio-economic status, Cole et al [35]

found that the risk of cystic disease increased with the value of the rent. This trend was not observed for fibroadenoma. Brinton et al [24] also observed that the lowest risk was seen in women with the lowest wealth category. In the population based study of Fleming et al [56] there was a trend towards lower rates of cystic disease and fibroadenoma in women, with low socio-economic status, (based on postal codes) although the trend was not statistically significant.

Soini et al [182] and Hislop and Elwood [81] have found no relationship between socio-economic status and risk. However, in the study of Hislop and Elwood the cohort studied was highly homogeneous economically and would render detection of a trend difficult. The study of Ravnihar and colleagues [156] is difficult to interpret because although there were significantly more peasants with cystic disease than controls (8% and 3%), there were also more professional women (17.5% and 15.6%), although the latter difference was not significant. Also, women with cystic disease tended to be better educated.

Brinton and her colleagues [24] make an interesting point that since the association of risk and socio-economic status is stronger for biopsied than non-biopsied BBD, then socio-economic status is a determinant of whether a lump is actually biopsied or not.

(f) Race

There is little clear information on risk of developing BBD and race. One of the earliest studies was conducted by Bertini & Ber in 1964 [12]. They studied 833 women who had attended Breast Cancer Centres in Israel, 428 of whom had breast disease, 130 with breast cancer and 298 with cystic mastopathy. These women formed 6 ethnic groups which, for convenience, were split into 2 classes. There were 'Western women' who were classified as women of European or American descent or who were born in Israel, and 'Islamic' women who were, as the name implies, women born in Islamic countries. The Western women had more breast cancer (17.9% compared with 7.5%) and cystic mastopathy (43.3% compared with 9.7%) than the Islamic women. Within the Islamic group it was found that Yemenite women had extremely low incidence of both breast cancer and cystic mastopathy. This low incidence was not due to the reluctance of Yemenite women to consult a doctor.

More recently in a population based study in Australia, Fleming et al [56] found that women born in Southern Europe had a significantly lower biopsy rate for benign mammary dysplasia than women born in Australia. A similar low rate was seen in women from Asia. The incidence of fibroadenoma was not significantly different in any of these countries.

Other studies have concentrated on the proportions of various benign breast lesions in black and white races. In 1972 Funderburk and co-workers studied the pathology of breast lesions in 2,552 black patients [65]. They reported that the predominant benign lesion was fibroadenoma, which comprised nearly 30% of all biopsies. Cystic disease was less than expected. However no information was given as to the age distribution of the population studied. In another series of breast biopsies of negro patients, Oluwole & Freeman [142] reported a predominance of fibroadenoma (48%) over cystic disease (24%). This contrasts with caucasian women where cystic disease is more prevalent, but, no allowance was made for the shifting pattern of disease with age. However, Silverberg et al [178] also reported a lower incidence of fibrocystic dysplasia in black patients.

In a study of post-mortem material from Japanese women and from Isei (immigrant generation) and Nisei (second generation) Japanese women living in Hawaii, epithelial hyperplasia was found in 18.7% of Japanese and 14.5% in Isei Japanese. However, in Nisei Japanese this percentage had dramatically risen to 51.4% [166]. In the investigation of Schuerch et al [170] material from 232 Japanese women was compared with that from 263 American patients. Using 14 morphological criteria they found that apocrine cysts, apocrine hyperplasia, intraductal hyperplasia, and atypical lobular hyperplasia were twice as common in the American material as the Japanese. The age distribution of these lesions was similar in both races. Solitary papillomas were twice as common in Japanese

women as in American women.

Since socio-economic status is also a strong factor in benign breast disease, it can be seen that what data there are could be explained partly, if not wholly, by differences in these factors.

(g) Oral contraceptives

It is generally accepted that women who take oral contraceptives have a reduced risk of BBD [191]. This is especially so in women who have been using them for more than 2 years [19, 24, 52, 81, 91, 92, 108, 110, 145, 156, 199]. Reductions of 25% and 65% have been claimed with greater than 2 years [145, 197], 50% after 5 years [108], and 80% after 8 years [52] of contraceptive use. This is consistent with Brinton's claim that the lowest risk was seen in women who had been using oral contraceptives for 8–10 years [24].

In this unanimity there are the dissenting voices of Sartwell et al [164] and Janerich et al [86], who report that they could observe no significant protective effect of oral contraceptives. They did observe that fewer women with BBD had used oral contraceptives, or had used them for a shorter duration, than controls, although these differences could have arisen by chance.

The protective effect of oral contraceptives extends to both cystic disease and fibroadenoma [24, 92, 145]. In the investigation by the Boston Surveillance Group [19], the protective effect was stronger for fibroadenoma. Brinton et al [24] found that the use of oral contraceptives was associated with a reduction in the incidence of unbiopsied BBD.

Since a woman with BBD has an increased risk of developing breast cancer (see page 6) it would be expected that oral contraceptives would be protective against breast cancer. However, most studies have shown that oral contraceptives have no influence on breast cancer risk [see 191]. Oral contraceptives reduce the incidence of fibrocystic disease if epithelial atypia is minimal or absent but have no effect in cases of marked atypia, and it has been suggested that this selective effect could explain the lack of protective effect against breast cancer [110, 149].

The mechanism by which oral contraceptives reduce the incidence of BBD is probably related to the progestagen component of the pill. The population study of the Royal College of General Practitioners [163] showed that the reduction in BBD incidence was correlated with the amount of progestagen in the formulation. This could explain why Nomura & Comstock [137] observed an increased risk of BBD in women using estrogens, notably diethylstilbestrol. Further details about the biochemistry of progestagens are given below (section Va). Part of the apparent protective effect of oral contraceptives may be artefactual. Thus, physicians may advise women who have had previous breast symptoms to use alternative means of contraception, thereby selecting a low risk group among oral contraceptive users.

(h) Methylxanthines

Methylxanthines include such compounds as caffeine, theophylline, and theobromine which are found in tea, coffee, chocolate, and colas. These compounds inhibit the enzyme adenosine 3′5′cyclic monophosphate phosphodiesterase, which degrades cyclic adenosine monophosphate (cAMP) to 5′-AMP. Cyclic AMP is of cardinal importance in the life cycle of cells, being involved in carbohydrate metabolism and acting as a 'second messenger' in the action of several hormones.

Minton and his collaborators, in a series of papers, have promoted the hypothesis that the ingestion of dietary methylxanthines can alter the concentration of tissue cAMP sufficiently to alter risk of both benign and malignant breast disease. The concentration of cAMP in human breast cancers is elevated [129], and the tissue levels of cAMP and cGMP (cyclic guanosine monophosphate) in benign breast lesions are 1.5 and 3 times, respectively, those found normally [127, 128].

Alterations in dietary habits have been reported to bring about clinical improvement of fibrocystic disease. Minton et al [127] observed that 13 of 20 women with fibrocystic disease experienced complete disappearance of all palpable breast nodules, pain, tenderness, and nipple discharge 1–6 months after commencing a caffeine-free diet. During this

time only 1 in 27 of the control group experienced a resolution of her disease. In a later and larger study, Minton et al [126] essentially confirmed their earlier results. The clinical results of Minton's group have been substantiated by other workers, although the beneficial effects were not as dramatic. Brooks et al [25] have reported that of 66 patients with fibrocystic disease, 88% showed improvement of symptoms and 91% a reduction in nodularity after adopting a methylxanthine-free diet. More recently, Ernster et al [51] randomized 158 women with benign breast lesions into two groups, one of which was recommended a caffeine-free diet. This diet group showed a 70% reduction in caffeine levels in breast fluid, indicating a substantial compliance to the dietary regimen. Comparison of the two groups showed a slight, but statistically significant, clinical improvement in the abstainers. These authors conclude that they are doubtful of the clinical usefulness of such a small benefit.

Whether methylxanthines are important in the etiology of BBD has yet to be resolved [79]. One of the main points in support of this thesis is the raised levels of cAMP in benign and malignant breast tumors. However, the results have been expressed as cAMP per unit weight of tissue. Since the cellularity of normal and tumor tissue are different, possibly a more appropriate measure of concentration would have been to express cAMP in terms of DNA. Hilf et al [80] have reported that the amount of DNA (per unit wet weight) in breast cancer tissue and tumors from fibrocystic disease was 4 and 1.5 times, respectively, that found in normal breast tissue. Had cAMP levels been expressed on a DNA basis, the differences cited by Minton and colleagues would not have been as impressive, and probably in the case of fibrocystic disease would have been indistinguishable from normal. Furthermore, in vitro studies have shown that elevation of intracellular cAMP stimulates the growth of human mammary epithelium whereas proliferation of mammary fibroblasts is inhibited [189].

On an epidemiological basis it is not clear whether women who present with BBD have an increased consumption of caffeine compared to non-affected women. Minton et al [126] found little to suggest that caffeine intake was significantly increased in women with fibrocystic disease. In the study of Lawson et al [105] only a modest positive association was found between hot beverage consumption and fibrocystic disease. Furthermore, in the studies of Ernster et al [51] and Lawson et al [105], there was no relationship between the amount of methylxanthines ingested and severity or incidence of BBD. Thus the risk of BBD was the same for women who drank 1–3 cups of hot beverage as those who drank 7 or more. However, in a recent study of Boyle et al [214] there was a significant positive association between caffeine consumption and fibrocystic disease. Those who consumed 31–250 mg per day had a 1.5 fold increase in risk whilst those whose intake was over 500 mg per day had a 2.3 fold increase in risk.

V Hormonal status of women with BBD

It is well established that some women experience premenstrual breast pain and swelling which can be so severe as to prompt medical intervention. Such changes point to a hormonal etiology and have led to much work to establish a possible relationship between abnormalities in the production of a variety of hormones and the occurrence of BBD.

(a) Estrogens and progesterone

The notion that the etiology of BBD is linked to ovarian hormones has been in the literature for 50 years. As an example, in 1931 Cutler reported the treatment of 'painful breasts' with ovarian residue [38]. However, it was not until 1939 that one of the first studies to determine the relationship between ovarian hormones and BBD was reported by Friedman et al [64]. Using crude bioassay methods, these workers reported no obvious abnormalities in the amounts of ovarian hormone excreted (see Table 5). However, Bucher and Geschickter in 1941 [27] reported low pregnanediol in women with chronic cystic mastitis and linked the disease with luteal phase dysfunction. Bacigalupo and his colleagues in a series of papers have reported evidence that the metabolism of estrogens was abnormal [6,

7, 169], but some of the evidence was based on the metabolism of massive amounts of administered estradiol benzoate or testosterone proprionate [8].

In 1974 Sherman and Korenman [175] described a 'luteal phase insufficiency' hypothesis in which they postulated that many of the epidemiological features of human breast cancer could be explained by the action of estrogen upon the breast unopposed by progesterone. Important in substantiating this thesis was the finding of Mauvais-Jarvis and his colleagues [121] that patients with BBD had a. subnormal production of progesterone during the luteal phase of the menstrual cycle. Progesterone modifies the action of estradiol in endometrial tissue by increasing metabolism of estradiol to estrone. This effect is mediated by an increase in estradiol dehydrogenase activity [194]. Progesterone also decreases the concentration of estradiol receptor [84]. There are data to suggest that these mechanisms could be involved in the etiology of BBD.

It was suggested that hyperplastic changes occur in the breast in the presence of estradiol if luteal progesterone secretion is deficient. The evidence for this comes mainly from the effects of estradiol and progesterone on endometrial tissue, which undergoes proliferation in the presence of estradiol whilst the combined action of progesterone and estradiol is to convert the tissue to a secretory state. It is generally believed that luteal phase insufficiency brings about endometrial hyperplasia and, in extreme cases, neoplasia. It was argued that in the breast, estradiol stimulates duct growth whilst progesterone halts this duct growth and promotes alveolar formation. Grattarola [70, 71] had previously reported that 60% of women with fibrocystic disease have endometrial hyperplasia, which supports the notion of a common etiology.

The evidence to support this hypothesis has come mainly from Mauvais-Jarvis and co-workers. They have reported that luteal phase plasma progesterone levels were significantly reduced in women with mastodynia, isolated cysts, fibrocystic disease, fibroadenomas, and increased nodularity of both breasts. The plasma estradiol levels were raised for all these categories, but this was only significant in women with fibroadenomas and increased nodularity [121].

Support for Mauvais-Jarvis and colleagues comes from the results of Balbi et al [11], Rolland et al [158], Martin et al [118], Marchesoni et al [115], London et al [112], and deBoever & Vanderkerchkhove [40], who found subnormal blood progesterone levels during the luteal phase in women with BBD. Balbi et al [11] claim that luteal phase function was deficient in 60% of BBD patients based on the frequency of values of progesterone which were less than 4 ng/ml on days 18 or 23 of the cycle. This assumed that in a normal cycle a value of greater than 4 ng/ml would be seen on both days, no allowance being made for variations in cycle lengths. The more logical question should have been what was the incidence of values greater than 4 ng/ml? This would have indicated ovulation had ocurred in 70% of the women studied. As these workers did not include control women in their study it is difficult to assess whether this frequency of ovulation was abnormal.

In contrast to the claims that progesterone is low during the luteal phase, England et al [50] reported elevated luteal progesterone in a small group of women with cystic disease aged 40–50 years. The third possibility that progesterone levels are normal, has been reported by Swain et al [186], England et al [50], Geller et al [67], and Walsh et al [198].

In the face of so much conflicting evidence the role of progesterone in the etiology of BBD remains undetermined.

Turning to the estrogens, most workers have found estrogen levels to be normal in women with BBD (Table 5). In a recent study by Reed et al [157] no abnormality was found in the plasma levels of estrone or estradiol in post-menopausal women with BBD but the amount of estradiol not bound to blood carrier-protein was significantly and abnormally raised. Unbound estradiol is thought to represent the estradiol fraction which is biologically available. BBD could be therefore the result of a hyperestrogenic stimulus even though the total blood level of estradiol is perfectly normal. Since women with breast cancer have also been reported to have increased amounts of biologically available estradiol [132], this raises the exciting possibility of a unifying theory of a common causal link between

Table 5. Ovarian hormones.

Measured	Number & pathology	Collection	Result	Investigator & date [Reference]
Urinary estrogens and P	60 BBD	4 × weekly interval	Normal	Friedman et al (1939) [64]
Urinary estrogen P2	7 Mastodynia 5 Adenosis 4 Cystic disease 7 Normal	Urines collected from day 11 onwards	Estrogen normal Pregnanediol low	Bucher and Geschickter (1941) [27]
Urinary E1, E2, E3, P2	15 Fibroadenomas 3 Others 18 Normal	Day 14 Day 21	P2 – normal Low E3/(E1 + E2)	Serban et al (1963) [174]
Urinary E1, E2, E3, P2	20 BBD	5 or 6 urines during cycle	Low luteal P2 High estrogens due mainly to E3	Mouravieva et al (1964) [135]
Urinary P2, E1, E2, E3	12 Fibroadenoma 4 Cystic disease 2 Other 24 Normals	Samples in follicular or luteal phase	No P2 abnormality % E1 low % E3 high relative to total estrogens	Marmoston et al (1965) [116, 117]
Urinary E1, E2, E3	47 BBD with breast cancer	1 × 24 hr urine between 18th and 23rd day	E1 + E2 + E3 higher in BBD	Bacigalupo and Schubert (1966) [8]
Urinary P2	30 Fibrocystic disease	–	P2 normal	Mirabile et al (1968) [130]
Urinary P2	105 BBD	–	P2 normal Short luteal phase	Maniulova & Pshenichnikova (1970) [114]
Plasma E2, P	43 BBD 56 Normal	One blood taken during day 6 to day 26	E2 normal P normal	Swain et al (1973) [186]
Serum E2	13 Cystic disease 32 Normal 18 Mastodynia	Every day over cycle	E2 high in luteal phase E2 normal	England et al (1974) [49]
Serum P	19 Fibroadenosis 13 Cystic disease 32 Normal	Every day of cycle	P normal P high in 5th decade during luteal phase in cystic disease	England et al (1975) [50]
Plasma E2, P	45 Mastodynia 29 Cystic disease 34 Fibroadenoma	One luteal phase sample	E2 normal P low	Sitruk-Ware (1977) [181]
Plasma E2	84 Fibroadenoma	One luteal phase sample	E2 high P low	Martin et al (1978) [118]
Serum E1, E2	12 Fibrocystic mastopathy	1 blood every week of cycle	E1 normal E2 normal	Golinger et al (1978) [68]
Urinary E1, E2, E3	35 Fibrocystic disease 48 Normal	1 urine per person	Normal E1, E2, E3	Bagli et al (1980) [9]
Plasma E2, P	22 Mastopathy 5 Normal	2 luteal and 2 follicular phase specimens	P low E3 low but not significant	Roland et al (1980; 1979) [158, 160]
Serum E2, P	35 BBD 181 Normal	One blood specimen at random	E2 normal P low in luteal phase	De Boever & Vanderkerckhove (1982) [40]
Serum P	384 Varying degrees of mastodynia 14 Controls	Luteal phase for 1 or 3 cycles	Luteal P normal	Walsh (1983) [198]

Table 5. (Continued).

Measured	Number & pathology	Collection	Result	Investigator & date [Reference]
Plasma E2, P	22 Micronodularity and mastodynia 10 Normals	Day 3, 6 and 9 of thermal plateau	E2 normal P low	Marchesoni et al (1981) [115]
Plasma E2, P	13 Mastodynia 24 Diffused mastopathy	18th and 23 rd day of cycle	60% have one P<4ng/ml	Balbi et al (1978) [11]
Plasma E1, E2, P	63 Fibrocystic disease	LH-RH and TRH stimulation test	Normal response	Geller et al. (1979) [67]

Abbreviations: P = progesterone; P2 = pregnanediol; E1 = estrone; E2 = estradiol; E3 = estriol; BBD = benign breast disease.

benign and malignant disease and could explain why some patients with BBD have an increased risk of breast cancer.

(b) Prolactin

The role of prolactin in the etiology of breast cancer has been discussed extensively [see 29]. Animal experiments have shown prolactin to be a very strong promoter of spontaneous and chemically-induced mammary tumors [18, 152]. It is not surprising that since the discovery of human prolactin over 10 years ago, and the development of a method for its measurement, numerous studies have been undertaken to determine the level of prolactin in women with both malignant and benign tumors of the breast (see Table 6).

The conclusion that can be drawn from the various studies using a single blood specimen per patient is that there is no obvious abnormality of prolactin concentrations.

Nevertheless, at least four studies have reported an abnormal prolactin release in response to TRH stimulation [67, 139, 215, 216]. It has been suggested that this could represent an increased prolactin secretion [216] although Kumar et al [215] in their thoughtful conclusion are more cautious as to the meaning of this phenomenon.

There have also been reports that the nycthemeral levels of prolactin are abnormal in women with BBD. Kwa and his colleagues [187] reported a peak of prolactin in the early evening in nulliparous women with BBD, which did not occur in parous women. Walsh and his colleagues [198] found that nulliparous women with mastodynia had elevated evening levels compared to parous women. These workers claimed that both parous and nulliparous women with mastodynia had elevated evening levels of prolactin. Halberg and co-workers have claimed that the 24 hour mean level of blood prolactin is abnormally raised in women with BBD [188]. In contrast to these reports, both Hoff et al [83] and Malarkey et al [113] found no abnormality in prolactin levels over 24 hrs.

Cole and his colleagues [34] monitored prolactin levels in the blood through the menstrual cycle and reported significantly raised levels for women with cystic disease and fibroadenosis for all phases of the menstrual cycle. The mean levels were 2–3 times higher than those found in controls. These authors, however, found no abnormality in women with breast cancer.

All these data show no clear abnormality in prolactin production in women with BBD. Thus any aetiological role that prolactin might have must be subtle or indirect, such as multiparity being associated with a lowering of night levels of blood prolactin [204].

(c) Androgens

The findings that women with breast cancer excrete subnormal amounts of urinary androgen metabolites [see 202] has prompted the question of the androgenic status in women with BBD. Over the past 20 years, it has been reported that women with BBD have low [23, 69], similar [48, 68], or higher [71] amounts of blood or urinary androgens than normal women (Table 7).

Table 6. Blood prolactin and benign breast disease.

Subjects and pathology	Results	Investigator & date [Reference]
10 Normal controls 12 BBD*	No difference	Boyns et al 1973 [20]
45 Premenopausal BBD 25 Post menopausal BBD 50 Normal	4 premenopausal and 2 postmenopausal patients had levels ≥25 ng/ml (normal level 6.5 ng/ml	Franks et al 1974 [62]
12 Cystic mastitis 32 Normal	No difference	Sheth et al 1975 [176]
150 Fibroadenoma 110 Cystic disease 330 Normal women	Both groups within the normal range	Franchimont et al 1976 [60]
4 BBD 10 Normal	TRH stimulation test: higher basal and stimulated levels	Ofuji et al 1976 [139]
5 Fibroadenomas 19 Normal	TRH stimulation test: basal BBD (18.9 ng/ml) not different from control (11.9 ng/ml); stimulated levels not different	Ohgo et al 1976 [140]
19 Fibroadenosis 12 Cystic disease 24 Normal	Sampled over menstrual cycle. Median values 0.1 mU/ml (controls), 0.15 mU/ml (fibroadenosis) and 0.2 (cystic). Significantly different.	Cole et al 1977 [34]
8 Fibroadenosis 8 Cystic disease 25 Normal	Indwelling needle and blood sampled over 24 hrs. No difference between BBD and control over 24 hrs.	Malarkey et al 1977 [113]
33 Mastopathy 15 Normal	No difference	Ozieblo 1977 [146]
12 Fibrocystic mastopathy	Not different from historical controls	Golinger et al 1978 [68]
11 Cystic disease & fibroadenoma 12 Normal	Sampled over 24 hrs: no difference	Hoff et al 1978 [83]
19 Mammary dysplasia 8 Fibroadenoma	Nulliparous women had evening peak of prolactin; but not parous	Tarquini et al 1978 [187]
63 Fibrocystic disease	LH-RH and TRH stimulation test: 30% of BBD gave high prolactin response.	Geller et al 1979 [67]
14 Mastodynia; 23 Cysts; 39 Fibrocystic disease; 18 Adenofibroma; 13 Lobular hyperplasia; 50 Normal	No difference between normal and any disease category	Mauvais-Jarvis et al 1979 [121]
9 Fibroadenoma 35 Fibrocystic disease 3 Normal	Mean levels were 32.9 ng/ml (fibroadenoma), 15.4 ng/ml (fibrocystic disease) and 9.2 ng/ml (controls).	Bahu et al 1980 [10]
78 Cystic disease 46 Microscopic cystic disease 42 Normal	Levels not significantly different, but high levels found in some women with BBD	Bischoff et al 1980 [14]
45 Fibrocystic disease 12 Others 45 Normal	Mean levels 538 mU/ml (fibrocystic disease), 376 mU/ml (others), and 250 mU/ml (controls)	Latteri et al 1980 [103]
25 Fibrocystic disease 11 Fibroadenoma 23 Normals	6 blood samples collected though 24 hrs: mean diurnal levels normal	Tarquini et al 1980 [188]
17 Mammary dysplasia 6 Normal	No difference and no change after vitamin E treatment	Sundaram et al 1981 [185]
47 Fibrocystic disease 105 Normal	No significant difference in mean but some higher (>20 ng/ml) levels in patients	Simkin 1982 [179]

Table 6. (Continued).

Subjects and pathology	Results	Investigator & date [Reference]
384 Varying degrees of mastodynia 14 Normals	Evening levels raised	Walsh et al 1983 [198]
21 Mastalgia 10 Nodular 11 Controls	TRH stimulation test: peak levels higher than controls for mastalgia and nodular group	Kumar et al 1983 [100]

* BBD = benign breast disease.

Of those claiming low levels, both Brennan et al [23] and Gorlich et al [69] stress that subnormal levels only occurred in the younger women (20–40 years). In addition, the study of Brennan and his colleagues reported a similar finding for plasma 11-deoxyketosteroids (11-DKS) and dehydroepiandrosterone sulfate (DHA-S). The conclusions of Mouravieva et al [135] are weakened because they present no data and merely state that urinary 11-DKS were 'somewhat decreased'.

The study of Marmoston et al [116], in which they found normal levels of urinary 11-DKS, can be criticised on the racial composition of the subject groups. Of the 18 women with BBD and 24 normal controls, 4 and 16 of each group, respectively, were white, 10 and 4 negro, and the remainder Mexican. In one of the two studies on androgens in blood in which normal levels have been found, England and his colleagues [48] have estimated DHA-S in samples taken throughout the menstrual cycle in an attempt to compensate for possible cyclic variation. This investigation had the disadvantage of having only 10 subjects in each study group, although a large number of estimations were performed.

Grattarola [70, 71] claims that women with BBD have supra-normal androgen levels. He found that there was a graded increase in the amount of urinary testosterone starting with the lowest levels in normal women, higher values in subjects with cystic disease plus moderate hyperplasia, and followed by the highest levels among patients with pronounced hyperplasia. There was also a gradation in the incidence of anovulation as judged by endometrial histology, the highest being in women with the most marked hyperplasia. Recently Secreto et al [172] reported a higher excretion of urinary androstanediol in women with mammary dysplasia. They also found testosterone excretion was normal, as did Jones et al [89]. However, the fact that more than 40% of urinary testosterone glucuronide comes directly from hepatic conversion of androstenedione, via dehydroepiandrosterone, and has not been in the general circulation makes the interpretation of urinary testosterone excretion difficult [96, 97]. Certainly blood testosterone levels seem to be normal since there is general agreement on this point [68, 201]. Furthermore, Jones et al [88] claim that not only are the total blood testosterone levels normal, but so are the amounts of biologically available testosterone, i.e. steroid not bound to blood protein.

One of the more recent studies on urinary androgen metabolites in benign breast disease has been reported by Pfaffenberger et al [153]. They determined the ratio of urinary etiocholanolone to androsterone and assumed it to be a measure of the relative activities of 5α and 5β oxidoreductase on testosterone. In a similar manner the ratio of tetrahydrocortisol to allo-tetrahydrocortisol was taken to reflect similar enzymic degradation of cortisol. Premenopausal women with BBD tended to have a subnormal etiocholanolone to androsterone ratio, whilst the postmenopausal patients tended to have a high ratio. Using both testosterone and cortisol ratios, the authors claimed that a significant number of postmenopausal patients had values never seen in normal women. It would be valuable if these interesting findings were confirmed.

Table 7. Androgens and benign breast disease

Hormone	Subjects and pathology	Result	Investigator & date [Reference]
URINE			
11-DKS	15 Fibroadenosis 3 Others	Normal	Serban et al 1963 [174]
11-DKS	20 Mastopathy	'Somewhat decreased'	Mouravieva et al 1964 [135]
11-DKS ANDRO ETIO	12 Fibroadenomas 4 Cystic disease 2 Others 24 Normals	Normal	Marmoston et al 1965 [116]
11-DKS ANDRO ETIO	63 BBD 21 Normal	Normal	Cameron et al 1970 [30]
11-DKS ETIO ANDRO DHA	39 BBD and 48 normals	Subnormal for patients aged 20–40	Brennan et al 1973 [23]
11-DKS ANDRO ETIO DHA	43 Mastopathia fibrocystica	Subnormal for patients aged 20–40	Gorlich et al 1975 [69]
Testosterone 5α-Androstane-3α, 17β-diol	11 Fibrocystic disease and moderate hyperplasia 15 Fibrocystic disease and marked hyperplasia 18 Normals	Testosterone and 5α-androstane-3α, 17β-diol increased	Grattarola 1978 [71]
Testosterone 5α-Androstane-3α, 17β-diol	39 Epithelial hyperplasia 22 Normal	Testosterone normal Androstanediol high	Secreto et al 1983 [172]
BLOOD			
Testosterone	14 BBD 19 Normals	Normal	Wang et al 1966 [201]
DHA-S	34 Benign breast disease	Levels same as in women with breast cancer	Brownsey et al 1972 [26]
11-DKS DHA-S	79 BBD and 52 normals 88 BBD and 192 normals	Subnormal for patients aged 20–40	Brennan et al 1973 [23]
Testosterone	12 Fibrocystic mastopathy	Normal	Golinger et al 1978 [68]
DHA-S	10 Cystic disease 10 Fibroadenosis 10 Normal	Normal over menstrual cycle	England et al 1981 [48]
Testosterone	20 BBD 45 Normal	Normal	Jones et al 1981 [88]

11-DKS = 11-deoxyketosteroids; ANDRO = androsterone; ETIO = etiocholanolone; DHA-S = dehydroepiandrosterone sulfate; BBD = benign breast disease.

Many studies devoted to the measurement of androgens in women with BBD can be criticized on the basis that little attention has been paid to the pathological category of the disease. However, even allowing for this there seems to be no clear abnormality in either the production of androgens or the excretion of their metabolites.

(d) LH, FSH, and TSH

The few reported measurements of TSH show no obvious abnormality in the urinary excretion or blood levels of this hormone in women with BBD. Tarquini et al [188] claimed normal serum TSH over 24 hrs in pre-menopausal women. Urinary TSH has been reported to be low, but only in the follicular phase of the menstrual cycle [102]. Basal and peak blood levels of TSH after TRH stimulation have been reported to be normal [100].

Although more work has been published on the gonadotropins, LH and FSH, the evidence for any abnormality is equivocal. Urinary LH has been claimed to be either low [114] or normal [130] whilst serum LH has been found to be either high [68, 185] or normal [90, 113]. Most authors have reported normal urinary and serum FSH [90, 114], although Mirabile et al [130] claimed that urinary FSH was low during the follicular and high in the luteal phase of the menstrual cycle. Urinary gonadotropins have been observed to be elevated [174].

The equivocal nature of these results is in keeping with those found for prolactin, suggesting no frank abnormality in the secretion of anterior pituitary protein hormones.

(e) Estrogen receptors

The proportion of breast cancers which have detectable cytoplasmic estrogen receptors has been variously quoted as being between 40%–80% [106]. This is substantially higher than that found for benign breast lesions [76]; taking all values in Table 8 the mean percentage is about 20%.

It is also apparent from this Table, that compared to other lesions, fibroadenomas have the highest proportion of estrogen receptors. This ranges from 11% [162] to 55% [3], the overall incidence being 38% (Table 8). This impression is reinforced by a series of 97 BBD samples studied by Menendez-Botet and colleagues [122], who

Table 8. Incidence of cytoplasmic estradiol receptor in benign breast lesions

Investigator & date [Reference]	Number of patients and disease	% ER+	Criterion ER+ (fmole/mgm cytoplasmic protein)
Feherty et al 1971 [53]	12 × FA	25%	0.3–0.6*
	27 × BMD	0%	
	2 × others	0%	
Leung et al 1973 [109]	17 × BBD	6%	1.7–14.6
Terenius et al 1974 [190]	35 × BBD	14%	Estradiol uptake into tissue slices
Hawkins et al 1975 [77]	19 × BBD	21%	0.12–0.54*
Leclercq et al 1975 [107]	8 × FA	50%	29–182
	10 × BMD	40%	34–157
Rosen et al 1975 [162]	27 × FA	11%	>10
	81 × BBD+	0%	
Singhakowinta et al 1975 [180]	9 × BBD	11%	>2
Menendez-Botet et al 1976 [122]	97 × BBD	7%	>10
Martin et al 1978 [118]	84 × FA	42%	>7
Allegra et al 1979 [3]	31 × FA	55%	>10
	16 × FCD	25%	
	8 × others	0%	

FCD = fibrocystic disease; FA = fibroadenoma; BBD = benign breast disease; ER+ = positive presence of receptor; BMD = benign mammary dysplasia.

* = fmole/mg tissue

+ = described as '... histologically 'benign' tissues ...'

found that of the 7 with estrogen receptors, 6 were fibroadenomas. On the reverse side of the coin, Feherty et al [53] and Rosen et al [162] examined 29 and 81 biopsy specimens, respectively, taken from patients with lesions other than fibroadenoma, and were unable to detect any with estrogen receptors.

It has been suggested that fibroadenomas have more receptors than other benign lesions because of their higher density of epithelial cells. However, Terenius et al [190] and Rosen et al [62] were unable to find any obvious relationship between the presence of receptor and the degree of cellularity, although Rosen et al [162] did comment that the three lesions with estradiol receptors were from fibroadenomas which 'were obtained from younger women and tended to have an abundant epithelial component'. Martin et al [118] claimed a significant correlation between receptors and cellularity. In 88 fibroadenomas classified according to receptor content there was a gradation of age and cellularity, the highest receptor content being associated with the youngest women and the highest cellularity. In a subsequent paper [119] these authors rung the changes and categorised these 88 fibroadenomas according to cellularity and, not surprisingly, found that receptor content and cellularity were positively related.

Cytoplasmic receptors for progesterone are also present in BBD tissue. Lloyd [111] found progesterone receptor in one sample out of 8 from women with fibrocystic disease. Of 88 fibroadenomas, 18% were found to have receptor to progesterone [119].

The amounts of estrogen and progesterone receptors (both cytoplasmic and nuclear) change considerably over the menstrual cycle [101]. Cytoplasmic and nuclear estrogen receptor content increase through the follicular phase, reaching a peak at mid-cycle, and then both fall during the luteal phase. The amount of cytoplasmic receptor is about 2 fmoles in the early follicular or late luteal phase with a mid-cycle value of 12 fmoles. Progesterone receptor in the cytoplasm starts at a high level (263 fmole/mg protein) in the follicular phase and declines steadily until the luteal phase reaching a level of about 5 fmoles. Nuclear receptor content appears to rise only during mid-cycle, remaining at a plateau during the follicular and luteal phases. It has been suggested that the increase in estrogen receptor in the first part of the cycle is because of the stimulatory effect of ovarian estradiol secretion, whilst the fall in receptors during the second part is due to the inhibitory action of luteal phase progesterone.

However, even with these large changes in receptor site content over the menstrual cycle, it is unlikely that these variations alter the conclusion that estrogen receptors are more likely to be present in fibroadenomas than other lesions, although cyclic variation might account for some of the quantitative differences reported.

(f) Prostaglandins

Rolland and his colleagues [158–160] have reported significantly raised plasma levels of prostaglandin E2 (PGE2) in 22 patients with BBD, compared with 5 normal controls, during both the follicular and luteal phases of the menstrual cycle. The amounts of plasma PGE2 in the patient group were similar for the two phases. These authors proposed that the increased PGE2 was a result of increased estrogen stimulation of the uterus, which was in turn a consequence of luteal insufficiency (see section Va).

Osteolytic prostaglandins are known to be released from breast cancers, and the question of whether they can be thought of as being ectopic tumor products has been discussed elsewhere [199]. Weight for weight, fibroadenomas release more prostaglandins in culture than breast cancers [47].Marx and colleagues [120] described hypercalcaemia in a woman with benign breast dysplasia in whom the symptoms were so severe that bilateral mastectomy was performed, after which there was a rapid and long-lasting remission of hypercalcaemia. The humoral agent produced by the benign lesion was not parathyroid hormone. The evidence suggests that the mediator of the hypercalcaemia was prostaglandin.

The finding of Rolland and his co-workers [158–160] that blood levels of PGE2 are raised in patients with BBD could be associated with an increased estrogen stimulus; however, the tumor itself may be producing prostaglandin.

(g) Metabolism of steroids by benign breast tissue

It has been claimed that breast cancer tissue has the ability to metabolize cholesterol to estrogens and progesterone, hormones of importance in mammary gland function. The ability of breast cancers to produce their own hormonal milieu prompted Adams and Wong [1] to describe such tissue as a paraendocrine organ. Although there is evidence that breast cancers can synthesize progesterone and estrogens from immediate precursors, it is doubtful that they can do so from a compound as metabolically remote as cholesterol [see 200].

There seems, however, to be no evidence on whether tissue from BBD has the ability to produce biologically important steroids. The main conclusion from what work has been done is that the potent androgen 5α-dihydrotestosterone can be produced from testosterone. In 1972 Jenkins and Ash found high rates of conversion of ^{14}C-testosterone to ^{14}C-androstenedione (1.4–18.4%). ^{14}C-5α-dihydrotestosterone was also formed, but to a lesser extent (0.3–1.0%), by 3 of the 5 tumors examined [87]. In the following year Miller et al [124] confirmed that fibroadenomas convert appreciable amounts of testosterone to dihydrotestosterone, significantly more than in breast cancers. They concluded that this difference was not due to a greater cellularity of fibroadenomas since the DNA contents were similar. Also, the conversion of dehydroepiandrosterone to testosterone was the same for both tissues.

Rose and colleagues [161] reported essentially the same results as Jenkins and Ash [87]. However, they extended the results by showing that the conversion of testosterone to androstenedione (or 5α-dihydrotestosterone) was greater in fibroadenomas than in tissue derived from patients with fibrocystic disease.

Tissue samples of fibrocystic disease when incubated with ^{3}H-progesterone yielded metabolites indicative of 5α-reductase activity. Comparison with normal and cancerous breast tissue showed the fibrocystic tissue to have the highest activity, with normal tissue having the lowest.

Estradiol 17β-hydroxysteroid dehydrogenase, the enzyme which converts estradiol to estrone, has been studied in fibroadenomas by Fournier et al [58]. Enzymic activity is highest during the luteal phase of the menstrual cycle, when there is direct association between cellularity and enzymic activity. During the follicular phase there is no such relationship. Progesterone topically applied to the breast before removal of the lesion led to a significant increase in enzyme activity. The dependence of estradiol dehydrogenase activity on progesterone is similar to that found to occur in endometrium [194].

VI Cyst fluid

One of the striking features to emerge from studies on cyst fluid is the high amounts of DHA-sulfate and androsterone sulfate present, compared with serum; in some cases there is a 1000-fold excess of these compounds in cyst fluid (Table 9). The corresponding non-sulfated compounds, DHA and androsterone, may also be present in high concentrations. Van Luchene and colleagues [217] have determined the structure and concentration of fifteen steroid sulfates and found that compared with blood, 5α reduced steroids were present in large amounts with 5α-androstane-3α, 17β-diol as a major androgen sulfate, its concentration being some 2000-fold that of blood. In contrast steroids such as cortisol, progesterone, and testosterone are present in similar concentrations to those found in blood (Table 9). The limited data on estrogens show that estriol-3-sulfate appears to be present in cyst fluid in appreciable amounts.

The concentrations of prolactin, LH, and TSH in cyst fluid are similar to those found in blood, although FSH seems to be lower (Table 10). The tumor marker human chorionic gonadotropin (HCG) was present in high concentration in about 35% of cyst fluid samples [22], whilst carcinoembryonic antigen (CEA) levels were high in all cyst fluids compared to blood [55, 143].

The immunoglobulins IgA, IgG, and IgM are present at levels of about 10% of those found in blood (Table 11). Witkin et al [209, 210] have also reported that amounts of IgA and IgG are low in cyst fluid. In addition these workers found that the

Table 9. Steroid concentration in cyst fluid.

Steroid	Cyst fluid	Blood	Reference
ANDROGENS			
DHA-sulfate (μg/dL)	20–30,500	60–100	[21]
	50–30,000	59–271	[4]
	60–46,200	–	[125]
Androsterone sulfate (ug/dL)	86–160,000	25–50	[21]
Androsterone (ng/dL)	0–950	20–50	
DHA (ng/dL)	0–200,000	40–1000	
Testosterone (ng/dL)	47.3 ± 45.9	40.9 ± 21.1	
Dihydrotestosterone (ng/dL)	151 ± 20.1	49.1 ± 35.0	
ESTROGENS			
Estriol-3-sulfate (pg/ml)	240–4310	9–76	[155]
Estriol-16-glucuronide (pg/ml)	19–153	–	
Estriol-3-sulfate, 16-glucuronide (pg/ml)	28–152	–	
Estriol (pg/ml)	12–30	–	
Estriol-3-glucuronide (pg/ml)	13–97	–	
OTHERS			
Progesterone (ng/dL)	514 ± 645	553 ± 740	[21]
Cortisol (μg/dL)	10.6 ± 3.5	12.9 ± 9.9	[21]
	0.2–7.5	6.2–18.1	[4]
Aldosterone (pg/ml)	43–288	65–204	[4]

Mean ± S.D.

Table 10. Protein hormone concentrations in cyst fluid.

Hormones	Cyst fluid	Blood	Reference
Prolactin (ng/ml)	4.3–80	4.1–76	[183]
	7.2–29	2.8–37	[22]
	0.6–37.2	4.4–20.2	[4]
LH (mIU/ml)	4.1–40.5	13.0–80	[183]
	2–125	7–125	[22]
FSH (mIU/ml)	1.0–4.4	2.55–80	[183]
	0–15	7–300	[22]
TSH (μU/ml)	1.00–12.25	1.00–6.35	[183]
HCG (ng/ml)	0.1–340	0.1–5.4	[22]
(mIU/ml)	0–846		[144]

IgA from 28% of 40 cyst fluid specimens was reactive with both the murine mammary tumor virus and Rauscher murine leukemia virus. In addition to the immunoglobulins IgA and IgG, Yap et al [218] have determined the concentrations of albumin, lactoferrin, and lysozyme in cyst fluid. They observed a wide variation in the concentration of these proteins, none of which were related to age, parity, or menstrual status.

Enzymes have also been detected in cyst fluid and, relative to serum, α-glutamyltranspeptidase and β-glucuronidase were present in extremely high concentrations (Table 11). Abnormally elevated levels of β-glucuronidase have also been found in benign lesions [41].

One of the most intriguing of the proteins found in breast cyst fluid has been described by Pearlman and colleagues [150] and is a component which binds progesterone. It is a glycoprotein with a molecular weight of 81,860 which is made up of 4 equal

sub-units. The protein does not bind cortisol, 17β-hydroxyprogesterone, or deoxycorticosterone. Pregnenolone binds to the protein at the same sites as progesterone. The protein is not progesterone receptor since the association constant is low (1×10^6 l/mol). The component was found in substantial quantities in a pooled sample of cystic fluid (9 mg/ml) relative to the total protein present (23 mg/ml) [150, 151].

In a recent publication, Friaria et al [59] described the presence of a transcortin-like protein in cyst fluid which could not be explained by simple contamination with blood transcortin.

The proteins in cyst fluid have been intensively studied by Haagensen and his colleagues [74, 75] using SDS polyacrylamide gel electrophoresis. They have separated four major proteins designated gross cystic disease fluid protein GCDFP-70, GCDFP-44, GCDFP-24, and GCDFP-15. The numerical suffix refers to the molecular weight, i.e. 15 means 15,000 daltons. GCDFP-70 was immunologically identical to albumin but present at one hundredth of the plasma concentration. A low concentration of albumin has also been reported by Fleisher et al [55]. GCDFP-24 was the most abundant component of cyst fluid and was immunologically identical to the progesterone binding protein described by Pearlman and colleagues. The GCDFP-15 protein was present in sufficient quantities in saliva and milk from normal women to be detected by immuno-diffusion using an antibody raised against GCDFP-15. Radioimmunoassay of GCDFP-15 has shown that 14% of normal women have plasma titres above 50 ng/ml. The percentage rises to 54% in women with unaspirated cystic disease. Patients with disseminated breast cancer have elevated levels of GCDFP-15 60% having levels in excess of 150 ng/ml. The compound was not elevated in the blood from patients with advanced cancer arising from sites other than the breast. The levels of both GCDFP-15 and CEA mirrored the response to treatment in patients with advanced breast cancer. However, in patients treated with the androgen fluoxymesterone, the concentration of GCDFP-15 was increased as a result of enhanced secretion of the protein rather than a change in tumor growth [45].

The ionic composition of cyst fluid has been determined by Fleisher et al [54] and Gatzy et al [66]. Generally, there was a high level of potassium

Table II. Proteins in cyst fluid.

	Cyst fluid	Blood	Reference
Carcinoembryonic antigen (ng/ml)	19–615	0.5–3.2	[55]
Non-detectable	0 out of 146	43 out of 146	[143]
<5 ng/ml	0 out of 146	103 out of 146	
<25 ng/ml	67 out of 146	0 out of 146	
>25 ng/ml	79 out of 146	0 out of 146	
IgG	101.9 ± 29.3*	0.11 ± 0.09**	[2]
IgA	25.6 ± 9.1	0.11 ± 0.09	
IgM	19.3 ± 8.5	0.15 ± 0.12	
IgG	3.3–14.5		[210]
IgA	1.5–7.8		
Lactic dehydrogenase	0–4**		[171]
Phosphohexose isomerase	0–4		
Lipase	0–4		
Alkaline phosphatase	0–4		
Amylase	up to 100		
γ-Glutamyl transpeptidase	up to 700		
β-Glucuronidase	up to 6000		

* Mean ± S.E.M. mg/dl.

** Ratio Cyst Fluid/Blood.

and a low concentration of sodium compared with serum. In some cyst fluids very high amounts of iron, zinc and copper were reported, although the range of results for these elements covered both the lower and upper limits found in serum. The concentrations of calcium, manganese, and phosphorous were similar to those found in blood.

The relevance of these compounds in cyst fluid to the etiology of BBD is unknown. Miller et al [123] have recently classified human breast cysts according to the concentration of electrolytes and androgen conjugates in the fluid. They found that the cysts fell into two distinct groups, and speculated that dividing cystic disease in this manner might reveal a subgroup with a high risk of developing cancer.

VII Tumor markers

The levels of blood CEA have been measured by various workers, and the results are shown in Table 12. Most workers have reported the CEA levels to be similar to those found in normal women. A notable exception is the study of Varnavides et al [195], in which women with BBD were reported to have almost twice as much CEA as normal women.

Franchimont et al [61] measured blood levels of α-fetoprotein, human chorionic gonadotropin (HCG), K-casein, and β subunit of HCG. In the 55 patients they studied, none had abnormal levels of α-fetoprotein or CEA. The other three markers were found to be higher than normal, each in one case. This gave an incidence of positivity of one cancer-related antigen in 5.5% of the patients. Tissue polypeptide antigen (TPA) is present in different types of malignant tumors and has been characterized by Bjorklund and Bjorklund [15]. This protein was found to be elevated in the serum of 27% patients with BBD, whilst none showed elevated levels of CEA. For comparison 53% of women with primary breast cancer had raised TPA levels [136]. In another report, Thynne and Greening [193] measured erythrocyte sedimentation rates (ESR) and found one patient with an ESR >20 mm/h or plasma CEA >20 ng/ml out of 8 patients studied. In a larger group of women with breast cancer, they reported a weak but significant linear correlation between CEA and ESR ($r = 0.31$; $P < 0.05$). Serum fucose was found by Wilkinson et al [208] to be in excess of 9.2 mg/mg protein $\times 10^{-4}$ in 20% (8) whilst CEA was positive in 17% (7) of patients.

Investigations on CEA in biopsy specimens

Table 12. CEA and benign breast disease.

No. of subjects or tissues studied	Result	Reference
BLOOD		
74	6 (8%) above upper limit of normal	[104]
17	1 (6%) above upper limit of normal	[184]
55	None with raised level	[61]
253	1 (0.4%) >5 ng/ml	[72]
50	Mean value = 21.8 ± 3.9 ng/ml Control = 12.2 ± 6.1 ng/ml (N = 14)	[195]
26	No values >2.5 ng/ml	[136]
8	1 (13%) >20 ng/mL	[193]
41	7 (17%) >2.5 ng/ml (non-smoker) or >5 ng/ml (smoker)	[208]
65	3 Cases (5%) ≥10 ng/ml. 6 Normals (3%) ≥10 ng/ml	[203]
TISSUE		
54	10 (19%) of tissue cytosols >3 ng/mg protein	[122]
43	2 (7%) of 28 examples of dysplasia were positive, the remainder negative	[177]
12	7 (58%) were positive, mainly non-proliferating epithelial cells	[212]
100	25% of fibroadenomas & 64% of fibrocystic disease were positive	[211]

show that up to 64% of tissue samples have CEA present (Table 12). Wittekind et al [211] claim that the highest incidence of CEA was found in tissue from women with fibrocystic disease, a category which may have an increased risk of developing breast cancer. However, Menendez-Botet and her colleagues [122] reported that of 54 benign tissue samples, CEA (>3 ng/mg protein) was found only in the cytosols of fibroadenomas (6) and tissue from patients with gynaecomastia (4). These authors also claimed a 85% concordance between the presence of CEA and estrogen receptor protein. These results, which show a high incidence of CEA in benign tumor tissue, are in keeping with the high levels of CEA found in cyst fluid.

VIII Conclusion

It is hardly surprising that no clear or consistent endocrine abnormalities have been reported in women with BBD. Translocation of an individual from 'normal' group to the 'benign breast disease' group depends to a large extent of the complaint threshold of the patient, and the safety threshold of the surgeon. This could largely explain the epidemiological data which show that risk of BBD (that is, a biopsy) is increased by family history of breast cancer and high socio-economic status, possibly in association with race. The inverse relationship with obesity may merely be due to an elevation of the threshold for the detection of benign breast lumps within adipose tissue. There is probably a stepwise and reversible progression of normal epithelium through atypia and hyperplasia and then on to in situ carcinoma, sometimes followed by invasive carcinoma. It is yet to be determined whether the steps in this progression are under hormonal control. Thus, it becomes necessary to study patients with proven epithelial hyperplasia and not to increase the noise/signal ratio by assaying blood and urine from women with the dubious risk factor of 'BBD'. Leaving aside methodological differences between laboratories, the inconsistencies in the literature may largely result from the heterogeneity of conditions within the BBD study groups.

Can there now be any justification for conducting endocrine studies on women whose condition has not been histologically defined? Fibrocystic disease is not a fore-runner of breast cancer, whereas epithelial hyperplasia probably is. This latter group require identification and close monitoring, in order to determine whether they exhibit a consistently abnormal pattern of hormone production such a subnormal androgen levels or elevation of free oestradiol. The patients should be followed in population studies in order to determine whether their risk factors such as family history differ from the normal population, and this group needs monitoring to compare their oral contraceptive usage with age and parity matched controls. Furthermore, do these patients show a consistent dysplastic pattern on mammography?

If a pattern of hormone abnormality can be determined in patients with biopsied epithelial hyperplasia, then this might be of value in detection of those 90% of breast cancer patients who have no prior history of BBD. Correction of such an abnormality might provide the first opportunity to prevent rather than treat the problem of breast cancer.

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