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Preface

This book is an attempt to bring together the available data concerning male breast cancer. What emerges is a piecemeal collection of reports all of which are unsullied by randomised controlled trials. These gaps in our knowledge about a rare disease will, I hope, act as a stimulant to collaborative efforts to improve the patient journey and the long-term outcome for men with breast cancer. I am most grateful to the following colleagues who kindly pointed out my more major errors and omissions:

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Chapter 1
The Problem

Abstract There is substantial evidence of deleterious health behaviour in males both in terms of high-risk activities and avoidance of contact with doctors. This manifests as delay in diagnosis and upstaging of disease with a consequent worsening of prognosis. The incidence of male breast cancer is rising worldwide and this is not just as a result of increasing lifespan in that age standardised rates are also increasing. Neonatal breast tissue demonstrates plasticity irrespective of gender. Normal male breast anatomy is similar to that of prepubertal females but is often overshadowed by the presence of gynaecomastia, particularly in the overweight. The lack of model systems including established human MBC cell lines has hindered research but with collaborative studies there is promise of better understanding and treatment for MBC in the future.

> *If thou examinst a man having bulging tumours on his breast and if thou puttst thy hand upon these tumours and thou findst them very cool, there being no fever at all when thy hand touches him, they have no granulation, they form no fluid, they do not generate secretions of fluid, and they are bulging to thy hand, thou shouldst say concerning him: One having bulging tumours: an ailment with which I will not contend* Fig. 1.1. Edwin Smith Papyrus. 17th century BC.

Introduction

Three thousand seven hundred years later, despite the advent of antisepsis, anaesthesia, cellular pathology and molecular biology, the outlook for men with advanced breast cancer remains poor. The ancient physician was correct, both in terms of the description of the disease and the dire prognostication. All is not gloom however: many men with early breast cancer treated promptly and correctly will live out their lives without recurrence.

Most men, when confronted with a personal diagnosis of breast cancer react with a mixture of concern and perplexity. Why have they developed a cancer normally associated with the feminine gender? What have they done, or not done, that has led to this potentially life-threatening disease? As with female breast cancer, epidemiology gives clues as to risk in the population but only rarely has been able to determine

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Fig. 1.1 The Edwin Smith surgical papyrus

individual predisposition. It is this combination of a disease regarded by many as exclusively affecting females together with a male propensity to avoid medical attention that can lead to a life-threatening situation.

Male Health Behaviour

There are very few men who consider themselves to be at risk of breast cancer so that their "breast awareness" is at best desultory and at worst cavalier in ignoring signs and symptoms that would send their female partners hastening to seek medical help. Ample evidence is available from many countries of a gender mismatch in health attitudes and behaviour. As an example, a questionnaire on Japanese oral health administered to 245 men and 282 women who were aged between 20 and 29 years revealed significantly better oral care in females as measured by frequency of brushing teeth, use of dental floss and dental check-ups [1]. A survey of 27,344 rural Austrians showed that men were less likely to exhibit safe health habits and more likely to manifest potentially dangerous risk behaviour [2].

When invited for a health check at an inner city general practice in Cardiff, 115/22 (51%) of women attended compared with only 101/253 (43%) of males [3].

When 26,078 Canadian adolescents were asked about use of alcohol, marijuana and other illegal drugs in relation to off and on road vehicle driving, 10% reported driving while under the influence and 21% had been driven by someone in that state. Most reporting this behaviour were males [4]. Slovenians completed a questionnaire relating to non-use of seat belts in the front and rear seats and the major risk factor for failing to wear a seatbelt was being male [5].

In a study of health-related practices and behaviour, a self-administered questionnaire was given to students at Khon Kaen University, northeast Thailand [6]. Of the 539 participants 155 were male and 384 female, the mean ages being 19.7 and 19.6 respectively. The females were more likely to eat fruit, clean their teeth, avoid fat and not smoke compared with the males. Female students had significantly better eating habits than men and coronary heart disease prevention was practised more frequently by women, particularly those in the medical faculty.

Doctors are not immune to this ostrich-like behaviour. In a Nepalese study examining prevalence of alcohol and substance use among students and junior doctors, 64% of males and 32% of females had indulged [7]. Cannabis smoking was confined to males. In a longitudinal study of doctors that started when they were medical students while although women reported more ailments than men they took less sick leave. Cutting across countries and ages this gender difference regarding health, lifestyle and proactivity characterises the frequent delay in seeking medical advice for male breast cancer.

Delay in MBC

The first large series of MBC cases came from the Memorial Hospital in New York and included 146 men with histologically confirmed carcinoma [8]. Of those with known country of origin and religion, 42% were Jewish. The symptom duration ranged from 2 days to 44 years and only 22% consulted a doctor within 3 months. During a 30 year period, 87 men with breast cancer were seen at MD Anderson Hospital and for the 40 with known symptom duration the delay was 12 months [9].

A large Danish series of 257 MBC cases reported a median delay of 6 months [10]. This reduction in symptom duration despite the relative age of the study could be a reflection of a well organised national health system, allied with improved health awareness. Ribeiro treated 292 males at the Christie Hospital Manchester and reported a reduction in delay with time [11]. For those treated between 1941 and 1961 the mean delay was 18.5 months compared with 11 months for those seen between 1962 and 1983. A later report from the Memorial Hospital indicated that the delay had reduced to 4.5 months [12], another from Wisconsin reported a median delay of 3 months [13] and a Canadian study showed a 4 month delay [14].

Five years after South Africa emerged from the apartheid era, Vaizey et al. reported that there was a considerable racial difference in length of delay [15]. For the 69 black patients the a median delay was 12 months, compared with 2 months for the 20 white and 2 Asian males. More recent work shows that in North Africa

Table 1.1 Median delay before consultation in MBC

Author	Number	Country	Delay in months (median)
Treves 1955 [8]	146	USA	9
Scheike 1973 [10]	257	Denmark	6
Yap 1979 [9]	87	USA	12
Ribeiro 1985 [11]	292	UK	1941–61 18.5 1962–83 11
Borgen 1992 [12]	104	USA	4.5
Donegan 1998 [13]	215	USA	3
Goss 1999 [14]	203	Canada	4
Vaizey 1999 [15]	91	RSA	Whites 2 months Blacks 12 months
Ben Dhiab 2005 [16]	123	Tunisia	8
Liukkonen 2010 [19]	58	Finland	6
Cutuli 2010 [20]	489	France	3
Bourhafour 2011 [17]	127	Morocco	28
El Beshbeshi 2012 [18]	37	Egypt	9
Ahmed 2012 [21]	57	Nigeria	11

Table 1.2 Advanced stage at presentation of MBC

Author	Number	Age (median)	Stage III (%)	Stage IV (%)
Schieke 1973 [10]	257	65.2	42	12
Gough 1993 [22]	124	62.5	35	11
Joshi 1996 [23]	46	64	13	10
Ben Dhiab 2005 [16]	123	65	63	29
Zhou 2010 [24]	72	61	39	3
Bourhafour 2011 [17]	127	62	50	29
Liu 2012 [25]		58	32	3
Teo 2012 [26]	21	68	43	19
El Beshbeshi 2012 [18]	37	58		92
Selcukbiricik 2013 [27]	86	62	30	5

Stage III, T1, N2/N3, M0, T2, N2/N3 T2, M0, T3, N2/N3, M0, T4, N2/N3, M0
Stage IV any T/N and M1

there is considerable delay ranging from 8 to 28 months [16, 17, 18]. In Western Europe there are delays of 3–6 months [19, 20], whereas in West Africa men wait for a median of 11 months [21]. These studies are summarised in Table 1.1.

Age and Stage at Presentation

The major risk factor for development of MBC is increasing age, as shown in Table 1.2 [10, 16, 17, 18, 22–27]. These series were sequential and not selected as having operable disease. The median age at diagnosis in these series was 62 years. Stage is

Table 1.3 Change in incidence of MBC with time

Country	Age adjusted incidence/ 100,000	
	1991–1995	2001–2005
England/Scotland	0.4	0.6
Canada	0.5	0.8
Australia	0.6	0.7

based on the TNM classification, and the proportion of MBC cases presenting with stage IV disease ranged from 3 to 92%. Considerable geographical variation is present. The highest rates of metastatic disease at diagnosis were reported from North Africa [17, 18, 19].

Incidence

The incidence of male breast cancer (MBC) is increasing worldwide. Combined results from England, Scotland, Canada and Australia reported an overall incidence of <1% with an absolute increase from 1991–1995 through to 2001–2005 [28]. World Health Organisation World Age Standardised Rates also rose as shown in Table 1.3. This suggests that the rise is not simply the result of increased life expectancy in men.

In a very large comparative study of female (FBC) and male breast cancer in 104 different populations, Kreiter et al. calculated age-adjusted incidence rates to examine the relation between rates of FBC and MBC [29]. The populations contributed >5 million person years of follow-up between 1998 and 2002 and each population was split into five age groups: <40, 40–59, 60–79, 80–99 years. Incidence rate ratios (IRRs) were derived, using a Poisson model, of breast cancer cases in each age group with an offset of log person years. The best fit was obtained with a random effects model. For each population there was a correlation between incidence of MBC and FBC (Spearman's correlation 0.54, $P < 0.0001$).

When the female populations were dichotomised into <50 years and ≥50 years and compared with the age adjusted incidence for all males the correlations were essentially unchanged, (<50, Spearman 0.49, $P < 0.001$, ≥50 Spearman 0.50 $P < 0.0001$). Most interestingly, when the incidence rate ratios for each 5 year group of men were compared with females the latter displayed Clemmesen's hook at age 50 whereas for males it was also present but at approximately 60 years.

Male Breast Anatomy

Mckiernan & Hull investigated breast size and lactation in both term and preterm infants and reported palpable breast nodules in the majority of mature infants of both genders [30]. In those term infants without palpable nodules most had a

complicated final trimester or problematic delivery. Of the under 31 weeks' infants none had palpable breast tissue at birth, but nodules and milk secretion occurred within a week of delivery in most. The majority of full-term infants lactated by age 7 days. The nodules persisted for up to 6 months and by that time sex differences had manifested. This suggests that neonatal breast development is at least partially dependent upon factors other than maternal hormones.

Anbazhagan et al. examined the epithelial phenotypes in the human fetal and infant breast autopsy specimens from 10 fetuses and 45 infants [31]. They used immunohistochemical staining for cytoskeletal proteins and κ-casein to define the evolution of the major cell types in both sexes from between week 16 and 24 months. They reported a characteristic cytoskeletal profile of apical cells in the lobular buds and terminal end buds. This implied that these may be stem cells with the capacity to become both basal and luminal cells.

Jolicoeur et al. examined basal epithelial cells from second trimester fetal breasts using immunohistochemistry [32]. Before and up to 20 weeks the mammary anlage was rudimentary with primary buds which may have been immature nipples rather than glandular tissue. This changed at 21 weeks when projections from enlarged primary buds extended into well-vascularized layers of dense mesenchyme. The basal cells in the projections were CD29, CD49f, CD104, keratin 14, vimentin, S100beta protein, and p63 positive suggesting a myoepithelial-like phenotype: Between weeks 21 and 25 many became keratin 17, alpha-smooth muscle actin, and CD10 positive. The basement membrane stained strongly for collagens type IV and VII, and laminin 5. There was strong basal staining for hemidesmosomal components indicating that most second trimester myoepithelial precursors might mediate local epithelial-mesenchymal interactions for orderly development and subsequent maintenance of homeostasis. This work does suggest that there is great cellular plasticity in breast development of both genders with errors in cell signalling possibly being partly responsible for subsequent development of malignancy.

In most men the breast tissue remains in the state of a prepubertal female, with slight development of retroareolar ducts and no lobules. The bulk of the tissue is fat, unlike the ductal and lobular glandular development of the post-pubertal female breast. Because there was little information on the configuration and location of the nipple-areola complex (NAC) in males, Beer studied 100 healthy men, aged between 20 and 36 [33]. The majority had oval NACs (91%), with seven having round NACs and two with asymmetry. The midpoint or the NAC was in the fourth intercostal space in 75% and over the fifth space in 23%. To locate the siting of the nipple two measurement were necessary: a horizontal line from mid sternal line to the nipple (line A) and a vertical line from sternal notch to intersection with line A (line B).

Model Systems

Despite the ability of breast cancer to grow in vivo it has been very difficult to achieve in vitro proliferation. There are now multiple established cell lines, most of which have been derived from malignant pleural effusions, the most famous being

MCF-7 [34]. These cell lines have enabled a myriad of investigations into hormonal and other facets of the biology of female breast cancer. No such resources have been derived from men with breast cancer and this has seriously compromised cell biology research on MBC. Caceres et al. implanted canine inflammatory mammary cancer (IMC) into 60 male and female mice aged between 6 and 8 weeks [35]. Cell lines 106 IPC-366 and SUM149 stses evolved more frequently in the males were injected subcutaneously. After 2 weeks, IPC-366 tumours grew in 90% of males and 100% of females. For those injected with SUM149 the respective tumour development was 40% and 80% respectively. Lung metastases evolved more frequently in the males and their tumors had higher levels of testosterone and estrone sulphafe compared with those in females. This might in time become an approach to the investigation of MBC but progress will only be possible when male cell lines have been developed.

Collaboration

Speirs et al. from the Leeds Institute of Molecular Medicine have set up the Male Breast Cancer Study Consortium and are collecting pathology specimens from MBC cases with the aim of producing tissue microarrays (TMAs) [36]. Specimens fom over 380 cases have been collected and this will form the nucleus of a very valuable resource. To date they have examined over 25 variables including receptors, and markers of proliferation, angiogenesis, and apoptosis.

At a multidisciplinary international meeting on MBC held at the National Cancer Institute, USA in 2008, the Breast International Group and the North American Breast Cancer Group united to form an International Male Breast Cancer Program [37]. The aim was to collect epidemiological and clinical data together with the formation of a tumor bank and to design clinical trials for MBC. First results have now been reported on 1473 MBC cases of whom 1384 were European and 89 American [38]. Median age was 68.5 years. Of those with M0 disease, 30% received neo-adjuvant chemotherapy. ER was strongly positive in 92% of tumours and using immunohistochemistry, 58% were luminal A, 35% luminal B/HER2neg, 6% luminal/HER2pos; 0.1% HER2 positive and 1% Triple negative. Such collaborations hold the greatest promise for improving our understanding and treatment for MBC.

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Chapter 2
Clinical Features and Diagnosis

Abstract Breast cancer is rare in men and most males referred to breast clinics will have benign conditions, frequently true or pseudo–gynaecomastia. For both genders, individuals with breast problems should have triple assessment (clinical evaluation, imaging and biopsy as indicated) in a specialist breast clinic. Ultrasound is the best initial imaging method for assessing the male breast and will differentiate between simple gynaecomastia and MBC in the majority of cases. Mammography is not required in all symptomatic males but should be added when there is a strong suspicion of breast cancer or the findings on clinical and ultrasound assessment are equivocal. Core biopsy is the method of choice for tissue sampling of masses and other suspicious findings in men. Before treatment all men with proven breast cancer should have bilateral mammography and ultrasound assessment of the axilla if these have not already been performed.

One man among a thousand I found. Ecclesiastes

Presentation

As would be expected, the commonest presenting complaint in MBC is a lump and in his series Treves reported that 72% had a mass with the next most common symptom being ulceration, present in 10% [1]. In a series of 257 cases from Denmark only 13% had a breast mass as a single symptom [2]. Pain is a presenting feature in up to 10% of men in the large series which have been summarised in Table 2.1 [1–5]. In Ribeiro's large series from Manchester, 81% complained of a lump and 10% had nipple retraction [3]. The largest national series of 489 Frenchmen with breast cancer reported that 83% had lumps, 7% had nipple retraction and 2% had nipple discharge [4]. In a Moroccan series the majority of the men had advanced disease and 98% complained of a lump with 2% having Paget's disease of the nipple [5].

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Table 2.1 Presenting features of MBC in large series

Author	n	Lump	Pain	Ulcer	Nipple retraction	Nipple discharge	Paget's	Other	Asymptomatic
Treves 1955 [1]	146	105 (72%)	19 (8%)	14 (10%)	11 (8%)	4 (3%)	2 (1%)	13 (9%)	5
Schieke 1973 [2]	257	182 (71%)	19 (8%)	17 (7%)	10 (4%)	9 (4%)	2 (1%)	13 (5%)	5 (2%)
Ribeiro 1985 [3]	301	244 (81%)	12 (4%)	18 (6%)	30 10%				9 (3%)
Borgen 1992 [6]	104	77 (74%)			18 (17%)	16 (15%)			
Goss 1999 [7]	229	196 (86%)	22 (10%)	18 (8%)	60 (26%)	20 (9%)		81 (40%)	3 (1%)
Cutuli 2010 [4]	489	403 (83%)			33 (7%)	11 (2%)		42 (8%)	
Bourhafour 2011 [5]	127	124 (98%)					3 (2%)		

Clinical Evaluation

The principles of clinical evaluation of men with breast symptoms are similar to those applied to females but with certain important differences. In terms of history-taking, after eliciting the presenting sign(s) and duration, a family history of FBC and occasionally MBC should be sought, together with ovarian or prostatic cancer. For the reproductive history those who are in a heterosexual partnership and have not had children should be asked whether this was out of choice. Prior testicular damage or undiagnosed Klinefelter's syndrome may be responsible for male infertility with an associated increase in risk of MBC. Many of these patients will be retired but their prior occupation should be sought since some such as blast furnace workers may have testicular malfunction due to a prolonged high ambient temperature.

Another important aspect of the history is use of regular medications since several of these may cause gynaecomastia. Risk factors for gynaecomastia are largely similar to those for MBC, including, increased aromatisation of androgens to estrogens in obesity, liver disease, testicular failure and testicular tumours, chronic renal failure and HIV. Details of drugs that have been implicated in increased risk of gynaecomastia are given in Table 2.2.

After inspection and palpation of the breasts, axillae and neck with the patient in the supine position, he is then asked to turn half on his side so that the examination can be repeated both facing towards and away from the examiner. Following the breast examination, the abdomen is palpated to determine whether hepatomegaly is present together with any signs of hepatic dysfunction. As a final part of the routine

Table 2.2 Drugs and gynaecomastia [10]

Definite cause	Probable association
Spironolactone	Risperidone
Cimetidine	Verapamil
Ketoconazole	Nifedipine
Human growth hormone (hGH)	Omeprazole
Estrogens	Alkylating agents
Human chorionic gonadotrophin (HCG)	Anti-HIV Efavirenz
Antiandrogens	Anabolic steroids
Gonadotrophin releasing analogues (GnRH)	Alcohol
5 alpha reductase inhibitors	Opioids

male examination the testes should be examined for signs of atrophy or tumour. If there is nipple discharge this should be tested for the presence of occult blood.

Many of these men will have gynaecomastia of variable extent. It is important to distinguish between pseudo-gynaecomastia which is lipomastia in the obese, without associated increase in glandular tissue, and true gynaecomastia in which glandular hypertrophy is present. Simon described three grades of gynaecomastia [8].

Grade I	Minor but visible breast enlargement
Grade IIa	Moderate breast enlargement without skin redundancy
Grade IIb	Minor breast enlargement with minor skin redundancy
Grade III	Gross breast enlargement with skin redundancy and ptosis

In 1958 Treves reported a series of 406 males with breast hypertrophy [9]. He pointed out that gynaecomastia is an ancient disease with statues of Pharaoh Seti I (1303–1290 BC) showing breast enlargement which would now be classified as grade III gynaecomastia Fig. 2.1.

Approximately 25% of men with gynaecomastia have developed the condition as a result of the medications that they are taking or the drugs that they are abusing. An evidence based review has categorised drugs into those that were definitely responsible and others with a possible association [10]. Spironolactone is a major offender producing gynaecomastia in 10% of men treated for severe cardiac failure [11]. Both spironolactone and cimetidine bind to androgen receptors producing an effective androgen blockade. For the majority of the agents there are effective alternatives which may reverse or reduce the gynaecomastia. The results are summarised in Table 2.2.

Ambrogetti reported a large series of 748 consecutive males patients referred for breast screening in Florence [12]. All had a clinical examination and mammography with sensitivities of 85% and 89% respectively. The average age was 50.5 years and cancers were found in 20 men (0.27%) of whom 17 were >60 years. Following biopsy 92 benign lesions were diagnosed of which 74 (80%) were gynaecomastia

Fig. 2.1 Pharaoh Seti I

cases. The combination of palpation and mammography had 100% sensitivity. The authors concluded that the diagnostic protocol used in females appeared to be fully effective in men. Hence triple assessment (clinical evaluation, imaging and cytology/core biopsy) should be the standard management for a man with a breast mass.

Imaging

1975 Kalisher & Peyster described xerographic manifestations of male breast disease, and in particular the distinguishing features of unilateral gynecomastia and MBC [13]. Gynaecomastia was characterised by increased ducts, ductal hyperplasia, stromal proliferation around small ducts and fatty replacement. MBC was usually central and dense, with irregular spiculated margins and sometimes skin changes or axillary lymphadenopathy.

Ouimet-Oliva reported radiological findings in 171 symptomatic men of whom 20 had MBC and 150 were diagnosed with benign lesions [14] (Table 2.3). They suggested a triad of diagnostic signs of MBC, namely a small mass, which was well defined and located eccentrically to the nipple. Dershaw et al. reviewed the mammograms taken on 23 men with proven breast cancer and found that the commonest

Table 2.3 Imaging investigation of symptomatic males

Author	Mammos	U/S	Biopsy	Benign	Cancer
Ouimet-Oliva 1978 [13]	**171**	**–**		**150**	**20**
Cooper 1994 [15]	**263**	**–**	**20**	**14**	**6**
Chantra 1995 [16]	**118**	**–**			**3**
Ambrogetti 1996 [11]	**748**		**110**	**92**	**18**
Gunhan-Bilgen 2002 [18]	**236**	**236**	**43**	**29**	**14**
Chen 2006 [19] Centre A Centre B Centre C	339 119 261	120 119 261	15 24 27	13 20 19	2 4 8
Patterson 2006 [20]	164	68			6
Muñoz Carrasco 2010 [21]	518	423	103	84	19
Adibelli 2010 [22]	164	164		147	17
Taylor 2013 [23]	679	364			25
Tangerud 2015 [24]	539	483	FNAC 261 Core 4	257	8

radiological sign was an uncalcified subareolar mass present in 72% [15]. Two men had a mass with associated microcalcification but not of the typical appearance seen in women with breast cancer. No evidence of the cancer was seen in 3 (13%) including one man with gynaecomastia which obscured the lesion.

Cooper reported that in a series of 263 symptomatic males, 66 (25%) had diffuse breast enlargement, 88 (33%) had pain and 20 (8%) had pain and swelling [16]. Mammographic findings were gynaecomastia in 213 (81%), solitary mass in 7 (3%) and multiple masses in 1 case. Chantra et al. carried out 118 mammograms on males during a 40 month period and found bilateral gynaecomastia in 66 (56%), unilateral gynaecomastia in 30 (25%), pseudogynaecomastia in 11 (10%), lipomas in 6 (5%), normal breast tissue in 2 (1%) and cancer in 3 (2%) [17].

In a large series of 748 consecutive symptomatic males seen in Florence, malignancy was diagnosed in 20 of whom 18 had invasive MBC, 1 had DCIS and the other a myxosarcoma [11]. Sensitivity was 85% for palpation, 89% for mammography, 94% for cytology and 100% for US with respective specificities of 95%, 94%, 96% and 98%. The combination of palpation and mammography achieved 100% sensitivity.

Applebaum et al. examined the mammographic findings in a series of 97 males with a histological diagnosis of breast disease which was gynaecomastia in 65 cases [25]. Of these 61 (94%) were diagnosed by mammographic signs as being nodular, dendritic or diffuse. Nodular gynaecomastia manifested as a fan–shaped density which radiates from the nipple. The dendritic variety comprised a retroareolar soft tissue density with extension into the surrounding fat. Diffuse gynaecomastia showed a mixed density similar to the adult female breast. There were 12 MBCs of which 3 (25%) had an associated DCIS component. On mammography the cancers were usually retroareolar masses sometimes eccentric and occasionally located peripherally. Margins could be well or ill-defined sometimes with spiculation and the shape was variously round, oval, irregular or lobulated. Additional signs were microcalcification

in 3 (25%), nipple retraction in 7 (58%)and skin thickening in 7 (58%). The authors concluded, although there were mammographic features of MBC which could be recognised, nevertheless there was considerable overlap between signs of benign and malignant disease.

Hanavadi et al. were prompted to ask "Is mammography overused in male patients"? [26] Because no protocols existed for the appropriate use of mammography in assessment of symptomatic males that it was likely that the investigation would be overused. They carried out an audit of all 220 male patients referred to the breast clinic at Cardiff University Department of Surgery between January 2001 and December 2003. Mammography was carried out in 134 (61%), usually before the patient was seen by a clinician. A total of four cases of MBC were diagnosed and in every case the diagnosis was suspected on clinical examination and subsequently confirmed histologically. It was concluded that mammography was unnecessary for most males and did not have a role in routine imaging.

Gunhan-Bilgen et al. described their experience of investigating 236 Turkish males both in terms of mammography and ultrasound [17]. There was a range of final diagnoses: gynaecomastia (206), MBC (14), fat necrosis (5), lipoma (3), subareolar abscess (2), skin cyst (2), haematoma (1), myeloma (1), and metastatic carcinoma (2). Of those with gynaecomastia 73 (35%) were dendritic, 71 (34%) nodular and 62 (31%) diffuse glandular. The 13 MBC manifested as a non-calcified mass in 12 (86%) and with calcification in 1 (7%). Gynaecomastia completely obscured the cancer in one case and partially in two others. The ultrasound findings were of irregular margins in 12 (86%) and well-defined margins in 2 (14%). This illustrated the value of ultrasound particularly in males where the cancer was obscured by gynaecomastia. Further evidence of the value of combined mammography and ultrasound was provided by Jackson et al. who reviewed the mammographic and ultrasonic findings in 41 men with breast enlargement [27]. Of the men 29 (71%) had both mammography and ultrasound, 9 (22%) had ultrasound alone and 3 (7%) had mammography without ultrasound. There were five cases with equivocal or suspicious findings on mammography but of the two that showed suspicious changes on ultrasound one proved to have MBC and the other had gynaecomastia on core biopsy.

Chen et al. reviewed results of mammography in 719 males seen at 3 different US centres [18]. Only one centre was using mammography and ultrasound in all cases. At mammography, MBC was typically a high-density irregular but well-defined mass. The margins could be spiculated, lobulated, or microlobulated and the majority are retro-areolar because the disease develops from central ducts.

Patterson et al. reviewed imaging and pathology results of 165 consecutive males evaluated over a period of 4 years [19]. Six (4%) proved to have MBC and mammograms were suspicious in all cases (100%). There were five invasive cancers and one DCIS. Mammograms were taken in 164 patients and 20 (12%) were reported as suspicious but 14 were benign. The sensitivity of mammography was 100% and the specificity 90% with a positive predictive value (PPV) of 32% and a negative predictive value (NPV) of 100%. Breast ultrasound was carried out in 68 (41%) and the 3 cancers were all seen as solid sonographic lesions. Ultrasound was responsible for 9/68 false-positive tests. Ultrasound had a sensitivity of 100% and a specificity of

74%. It was concluded that a normal ultrasound confirmed the negative predictive value of a normal mammogram.

Muñoz Carrasco et al. reported a large series of 628 Spanish males assessed between 1993 and 2006 [20]. Of these 518 had mammograms and 423 were investigated with ultrasound. There were 19 MBC, 526 with gynaecomastia, 84 benign conditions and 25 diagnosed as normal. Of the imaging modalities, mammography was the most sensitive (95%) but ultrasound was more specific (96%).

Adibelli et al. reported a series of 164 Turkish men, all of whom had mammography and breast ultrasound [21]. Biopsy was carried out in 75 (46%) with the remainder being diagnosed radiologically. There were 13 cancers (8%), 147 patients with gynaecomastia (90%), and other diagnoses included fibroadenoma (1), fibrocystic change (2), and skin cyst (1). Clinically, 2 MBC (15%) were deemed to be benign and mammographically 11/13 (85%) were visualised. Microcalcifications were seen in one case (9%). Margins were irregular in 9 (82%) and well-circumscribed in 2 (18%). Seven lesions (64%) were retroareolar and 4 (36%) were eccentric. Nipple inversion was seen in 5 (45%), and skin thickening 4 (36%). All of the malignant masses were identified with ultrasound, albeit one retrospectively after mammograms had been reviewed. All of the cancers were solid and hypoechoic with irregular margins in 11 (85%) and smooth margins in 2 (15%). Posterior shadowing was present in 5 cases.

Doyle et al. reported the imaging characteristics of 20 MBC collected over 10 years [28]. The majority, 16, were invasive ductal carcinoma of no special type and the others were invasive papillary, invasive lobular, undifferentiated invasive cancer and in situ papillary carcinoma. Most of the cancers were grade 2 but there was no relation between grade and tumour image. Mammography was carried out in 13 patients and all showed a mass which was ill-defined mass in 6 (46%), spiculated in 5 (39%), and well-defined in 2 cases. Nipple retraction was present in 4 (31%) and 2 masses (13%) showed flecks of calcification. Gynaecomastia was present in 5 (39%) but this did not mask the cancer. Ultrasound was performed on 14 patients and a mass was visualised mass in 13 (93%). In the case without a discrete solid mass, a cyst with associated duct dilatation was observed. All the cancers were hypoechoic compared with normal tissue. The mass was ill-defined in 8 (82%). well-defined mass in 3 (23%) and spiculate in 2 (15%). Acoustic through-transmission was unaffected in 8/13 (62%), 3 (23%) had posterior shadowing, and 2 (15%) displayed posterior enhancement.

Taylor et al. audited the value of triple assessment used in 1141 males seen at the Cambridge Breast unit between 2001 and 2009 [22]. The age range was 29–89 and all aged ≥35 years underwent mammography. During this time 25 MBC were diagnosed and most (24) in men aged >40, with one 1 aged 29 years. The young patient was diagnosed with a combination of clinical evaluation and ultrasound whereas the others were suspected clinically or had suspicious mammograms which led on to ultrasound and biopsy. The sensitivity of clinical evaluation was 64%, with a specificity of 99%, PPV of 76% and NPV of 99%. For mammography the sensitivity was 78%, specificity 99%, PPV 79% and NPV 99% and 92%, whereas ultrasound had a sensitivity of 92%, specificity 97%, PPV 88% and NPV 99%.

Because of the typical appearance of gynaecomastia on mammography, Tangerud et al. investigated the necessity for ultrasound and FNAC under these circumstances [23]. They reviewed the radiological images of 539 male patients together with the ultrasound reports of 483 and cytology reports of 336. Gynaecomastia was present in 350 cases of whom 340 (97%) had ultrasound and 261 (75%) had FNAC. Core biopsies were taken from 4 (1%) patients. There was no change in diagnosis in any of the patients who had ultrasound and or FNAC. They concluded that ultrasound and FNAC is superfluous when classic mammographic signs of gynaecomastia are present and contributes to unnecessary costs. An alternative view is that if ultrasound shows classic signs of gynaecomastia then mammography is unnecessary, again reducing the cost of assessment.

Breast MRI

Blaumeiser et al. were the first to use MRI in the investigation of a male with intracystic papillary carcinoma of the male breast [29]. This was followed by a report from Tochika et al. concerning the use of MRI in the pre-operative workup of a 66-year old male who proved to have an intracystic breast carcinoma [30]. The MRI displayed a fluid level on T2 weighted images and the time signal intensity rose sharply and peaked at 3 min suggesting malignancy. Subsequently MRI was used to assess various other rare male breast diseases including haemangioma [31], pleomorphic lobular carcinoma [32], chondrosarcoma [33], pilomatricoma [34] and myofibroblastoma [35].

Morakkabati-Spitz et al. performed the first prospective study on 17 consecutive male patients with a palpable breast lump [36]. All had mammography, breast ultrasound and dynamic breast MRI, using a standard protocol involving a T2-weighted turbo spin-echo sequence and a subsequent dynamic series. In all, 24 breast abnormalities were identified by MRI. MBC was diagnosed in 3/17 patients (18%) with a total of 5 cancers being seen. Gynaecomastia was present in 11 and was unilateral in 6 cases. Other diagnoses were pseudogynaecomastia (2) and angiolipoma (1). The MBC were all irregular with a mixed internal architecture and displayed rapid initial enhancement followed by a washout phase (BI-RADS category 5). In contrast diffuse and nodular gynaecomastia was associated with slow initial and persistent enhancement (BI-RADS category 2) in 10/11 cases. The other patient who had histologically conformed bilateral gynaecomastia manifested an area of segmental enhancement deemed suspicious for DCIS. There was no enhancement in pseudogynecomastia and the angiolipoma demonstrated slow initial and persistent enhancement (BI-RADS category 2). It was concluded that male breast cancer displayed similar MRI characteristics to those seen in FBC.

Shaw et al. described 72-year-old man who was having regular mammograms after a left mastectomy for a grade II ductal cancer that was ER/PR+ve [37]. After he had taken adjuvant tamoxifen for 4 years mammography demonstrated a new 6 mm retroareolar opacity. Clinical examination and ultrasound did not reveal any

mass. He underwent contrast-enhanced MRI which showed a 6 mm nodule of decreased signal intensity on the T1-weighted images and increased signal intensity on the Short-T1 Inversion Recovery (STIR) images. Following intravenous gadolinium injection there was rapid early enhancement and washout, consistent with malignancy. Repeat ultrasound identified an isoechoic solid nodule, confirmed by core biopsy to be a grade I cancer, treated by total mastectomy.

When reviewing the assessment of symptomatic males, Hines et al. from the Mayo Clinic argued that mammography should be performed if clinical findings were indeterminate and ultrasonography as an adjunct to mammograms [38]. They opined that no evidence supports the use of MRI in male breast patients and this is in agreement with the available evidence.

[18]F-FDG PET/CT

If the evidence regarding the use of breast MRI is minimal, that for [18]F-FDG PET/CT is even more scanty. Ramtahalsing et al. reported a false positive [18]F-FDG PET/CT uptake in a male with gynaecomastia [39]. Groheux et al. reviewed their experience of [18]F-FDG-PET/CT in staging, restaging, and therapy response assessment based on 30 scans performed in 15 MBC cases [40]. Of the 30 investigations, 7 were part of initial staging, 11 for restaging and 12 for monitoring response to treatment. For detection of distant metastases the sensitivity of PET/CT sensitivity was 100%. The specificity was 67%, PPV 86%, NPV 100% and accuracy 89%. In 40% of studies PET/CT yielded more information than conventional imaging including bone scans, chest radiography or tomography, and contrast enhanced-computed tomography (CE-CT) of abdomen and pelvis. As a result, treatment was changed in 13/30 cases (43%), indicating that this expensive and often unavailable modality was a powerful addition for staging, restaging and response assessment in MBC.

Evangelista et al. re-interpreted 31 FDG PET/CT scans of 25 MBC cases investigated in two Italian centres [41]. PET/CT scans were performed for initial staging (5) restaging (22), response to therapy (2) and as part of follow-up (2). No evidence of cancer was found in 10 subjects but present in 15 (60%). For those undergoing staging, there was significant uptake in the primary in 4/5 and 3 of these had lymphatic and distant metastases. When used as part of re-staging setting, PET/CT surpassed conventional imaging for detection of distant disease and resolved 2 false-positive results.

Vatankulu et al. examined the histology and immunohistochemistry in 15 MBC who had also had preoperative PET/CT [42]. There were no significant differences between patients classified histologically or by immunohistochemistry in terms of maximum and average standardized uptake values (SUVmax and SUVavg), metabolic total volume, and total lesion glycolysis (TLG. In those patients with distant metastases SUVmax, SUVavg, and TLG were significantly elevated compared with men who did not have distant metastases. Although there was no correlation between tumour characteristics and F-FDG PET/CT findings nevertheless it was concluded that PET/CT gave reliable information on tumour size and axillary nodal status.

Fine Needle Aspiration Cytology (FNAC)

Gupta et al. reported an extensive experience with of 7,231 breast needle aspirates of which 99 were from males [43]. MBC was diagnosed in four cases and gynaecomastia in 61. It was stated that although the clinical differentiation between gynaecomastia and MBC could sometimes be difficult this was overcome when carrying out FNAC. Sneige et al. reviewed the MD Anderson Cancer Center of 64 FNAC specimens, including 33 patients with prior extramammary cancer [44]. The cytological diagnoses were gynaecomastia (45), MBC (6), metastases (5), possible cancer (1), intra-mammary lymph node (1), and lipoma (1)., with 5 non-diagnostic aspirates (Table 2.4). Of the 6 cases originally diagnosed as MBC 2 were found to be secondaries, mesothelioma and mucinous adenocarcinoma of unknown primary (1). There were no false-positive diagnoses.

Lilleng et al. reported 241 males who underwent FNAC and of these 27 (11%) were non-diagnostic [45]. There were 8 MBC cases diagnosed cytologically and 200 men with a benign cytological diagnosis were confirmed at follow-up. No cancers developed on follow-up of the benign cases and all 8 MBC diagnoses were confirmed histologically. It was concluded that the high rate of surgical biopsies of benign male breast lumps could be largely avoided by use of FNAC. In a study from Kuwait, Das et al. investigated 188 males with breast lesions between 1988 and 1993, and were able to review the cytology in 185 cases [46]. There were 132 cases with gynaecomastia, 16 other benign lesions, 5 inflammatory lesions and 6 MBC. The diagnostic accuracy for gynecomastia was 100%, other benign lesions 100% and for MBC 67%, there being one benign lesion which was reported as highly suspicious on cytology.

Vetto et al. carried out a prospective study of clinical valuation and FNAC in symptomatic males seen in three breast clinics [47]. There were 51 men with unilateral breast lumps and 13 had mammography. Both clinical evaluation and FNAC were scored as benign or suspicious and a suspicious lumps were excised. In 6 cases both tests were suspicious and this was confirmed histologically. Benign results of both tests occurred in 38 cases. There were 7 men whose tests were not in agreement and all were biopsied with benign results. There were 5 false positive cases on clinical evaluation and 2 from FNAC. In this series mammography added nothing to the combination of clinical evaluation and FNAC.

Table 2.4 Results of FNAC from male breast lesions

Author	N	C1	C2	C3	C4	C5
Gupta 1991 [43]	99	12	82	–	2	4
Sneige 1993 [44]	64	5	47	–	1	11
Lilleng 1995 [45]	241	27	206	–	–	8
Das 1995 [46]	188	26	156	–	–	6
Vetto 1998 [47]	51	0	43	–	–	8
Joshi 1999 [48]	507	114	323	–	–	70
Westenend 2002 [49]	153	13	125			15

Joshi et al. reported 19 years of experience with breast cytology which included 507 specimens taken from males [48]. MBC was diagnosed in 70 (14%) and 114 specimens were non-diagnostic. There were 295 benign results (58%) and 29 (6%) which were indeterminate (5.7%). A total of 114 FNACs (22.5%) were unsatisfactory. Histology was obtained in 97 cases and there were no false positive or false negative diagnoses giving 100% sensitivity, specificity and diagnostic accuracy for FNAC. Westenend et al. reviewed 153 male breast FNACs taken between 1985 and 2000, of which 141 were derived from unilateral lesions [49]. The non-diagnostic rate was 13% giving a sensitivity of 87% and specificity of 78%. If the inadequate cases were excluded sensitivity was 100% and specificity 89% with a PPV of 100%.

Core Biopsy

Because of concerns that a cytological diagnosis of malignancy does not amount to a diagnosis of invasive cancer, most centres now carry out core biopsies before proceeding to surgery in order that appropriate management of the axillary nodes can be instigated. Additionally in men with stage III or IV disease knowledge of ER/PR/HER2 status indicates the most appropriate form of neoadjuvant or palliative therapy. Between 1998 and 2003 Janes et al. took needle core biopsies from all men with unilateral breast swelling whenever the diagnosis was indeterminate [50]. Of 113 patients, 93% had gynaecomastia, two patients had MBC and one had metastatic lymphoma. Westenender reviewed results of 26 core biopsies taken from males with unilateral masses between 1993 and 2002 [51]. There were 6 malignant specimens, one of which was described as small cell carcinoma. Gynaecomastia was confirmed in 13 cases only one of whom had further surgery and 7 proved to have benign breast conditions. They concluded that core biopsy of the male breast was an accurate method of making a pre-operative diagnosis.

Bazzochi et al. took core biopsies from 31 male patients and 7 (23%) lesions were MBC and 24 (77%) were benign [52]. For patients with clinically suspected malignancy and those with *BRCA2* mutations or prior breast cancer) malignancy was confirmed by core biopsy in all cases. All cancers seen on mammography (4/7) presented as a mass whereas the majority of benign lesions (21/24) showed less specific increased density.

Bicchierai et al. reported the experience of University of Florence in terms of preoperative histological diagnosis on 131 males who underwent core biopsy of suspicious male breast lesions [53]. They found that core biopsy was an accurate technique for distinguishing between benign and malignant masses and suggested that it should form part of the assessment of unilateral male breast lesions. These relatively limited data unanimously support the accuracy of core needle biopsy in making a pre-operative or pre-treatment diagnosis of MBC.

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Chapter 3
Risk Factors

Abstract Age is a major risk factor for MBC with Clemmesen's hook present on the age-incidence curve. Male/female incidence ratios are highest sub-Saharan Africa possibly as a result of the one in eight incidence of hepatitis B. There is an up to threefold increase in MBC risk for those of higher versus lower sociodemographic status. Of MBC cases, 7.5% have Klinefelter's syndrome there is a 50-fold increased risk for males with the syndrome. Transsexuals taking estrogens are more likely to develop MBC at an early age but approximately 50% of these tumours are ER−ve.

There appears to be no association between smoking or alcohol intake and risk. Although obesity increases risk of MBC no association between diet and risk has been found. The standardised incidence rates for various occupations have shown an increased risk for workers in sawmills and blast furnaces possibly because higher ambient temperatures inhibit testicular function. Increased risk of MBC follows mumps orchitis, epididymitis and undescended testis. There is an increase in risk of both FBC and MBC in those treated by total body irradiation form childhood Hodgkin's disease and acute lymphoblastic leukaemia. Among male Japanese survivors of the atomic bombing there was a 15-fold increase in relative risk of MBC. The minimal number of MBC cases in HIV positive men indicates that this is not a major risk factor.

It is incident to physicians, I am afraid, beyond all other men, to mistake subsequence for consequence. Samuel Johnson

Age

Multiple risk factors for MBC have been described and studied and these fall into two main groups, non-modifiable and modifiable. The former include age and ethnicity and in common with the majority of solid tumours increasing age is a major risk factor for MBC. Anderson et al. analysed data from the Surveillance, Epidemiology and End Results (SEER) to compare 5494 MBC with 835,895 FBC cases and reported that the median age at diagnosis was 67 for the former and 61 in

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the latter group [1]. When age specific incidence rates were plotted there was a striking difference between males and females. There was a rapid rise up to age 50 in women with an inflexion at age 50 (Clemmesen's hook) and then a slower rate of increase. For MBC the rate rose steadily so that with advancing age there was narrowing of the male/female incidence ratio.

Kreiter et al. analysed 104 different populations including North America, Europe, Russia, Asia and Australasia [2]. Age-adjusted incidence rates were calculated for both MBC and FBC in each population to compare 5-year age group incidence rates for both males and females. They found a worldwide correlation between incidence rates of FBC and MBC which was highly significant when MBC was compared with that in women aged ≥50 and also those <50. Clemmesen's hook was also seen in males, albeit to a lesser extent but at age 60 rather than 50 for females.

Ethnicity

There are wide geographical variations in male/female incidence ratios, with the lowest in Western countries and the highest in Africa. Using data from *Cancer in Five Continents*, Ly et al. compared international incidence rates in MBC and FBC based on 8681 and 1140,00 cases respectively [3]. The lowest ratios were found in Israel (70) and Iceland (84) with the highest ratios in the UK (153) and Japan (169).

The situation regarding risk for ethnic groups within one country is more complex. When Anderson et al. compared age-adjusted incidence trends rates in SEER data from 1973–2005 they stratified the FBC by age <50 and age ≥50 and found that the trend was stable in males but increasing in females [1]. The male/female incidence ratio was higher among the black cases.

In the 2013 US Census, 78% of the population described themselves as white, 17% Hispanic and 13% were black. There has been a series of publications from the US describing the ethnic background of MBC cases based largely on SEER or Veterans Administration data [4–7]. These are outlined in Table 3.1 and suggest that there is no over-representation of African American MBC cases.

Table 3.1 Ethnicity and MBC risk

Author	N	Source	Accrual	White	Black	Other	Unknown
Nahleh 2007 [4]	612	VA	1995–2005	458	144	1	9
Klein 2011 [5]	4186	SEER	1988–2006	3504	493	188	1
Fields 2013 [6]	4276	SEER	1973–2008	3539	494	243	–
Shin 2014 [7]	4279	SEER	1988–2010	3266	552	461	–
Total	13,253			10,767	1683	893	10
Percentage				81%	13%		

There is however a lot of anecdotal information suggesting an increase in risk of MBC in Africa. Series reported from Sub-Saharan Africa are outlined in Table 3.2 and show an increased ratio of MBC/FBC cases compared with the western world with 1.9–8.9% of mammary malignancy occurring in males [8–21]. Amir et al. examined incidence rates in Tanzania both before and during the AIDS epidemic which started in 1983. After 1982 there was a fall in the number of MBC cases but a rise in FBC. There was a significant widening in the male-female ratio which fell from 0.09:1 to 0.03:1.

In North Africa a different pattern emerges as is shown in Table 3.3. El-Gazayerli and Abdul-Aziz from Alexandria reported a high incidence of MBC which may have resulted from endemic bilharziasis (schistosomiasis) which was known to have affected seven out of eight of the traceable MBC cases [22]. After penetration of the skin *S. mansoni* migrates to the liver, feeding off erythrocytes, growing up to 1 cm in length and damaging the liver with ensuing hyperestrogenisation. A similarly large proportion of MBC was reported from Sudan, where 15% of the population suffer from schistosomiasis [23]. Similarly in Ethiopia almost 14% of breast cancer cases were male [24]. A subsequent much larger Egyptian study reported that MBC comprised only 0.89% of total breast cancer cases [25]. MBC rates in Morocco, Tunisia and Libya were slightly elevated compared with Europe [26–28].

Table 3.2 Male-female breast cancer incidence in Sub-Saharan Africa

Author	Location	MBC (%)	FBC
Ajayi 1982 [8]	Lagos , Nigeria	12 (2.4%)	488
Aghadiuno 1987 [9]	Ibadan, Nigeria	43 (3.4%)	1232
Sano 1987 [10]	Burkina Faso	5 (4.1%)	117
Hassan 1995 [11]	Zaria Nigeria	16 (9%)	162
Adeniji 1997 [12]	Ile-Ife Nigeria	10 (1.9%)	503
Amir 2000 [13]	Tanzania	117 (5.25%)	2111
Chokunonga 2000 [14]	Zimbabwe	2 (0.8%)	124
Dogo 2004 [15]	Maiduguri, Nigeria	11 (3%)	284
Kidmas 2005 [16]	Jos, Nigeria	26 (8%)	276
Oguntola 2009 [17]	Osogbo, Nigeria	7 (8.9%)	72
Rachid 2009 [18]	Naimey, Niger	22 (5.7%)	364
Olu-Eddo 2010 [19]	Benin, Nigeria	16 (2.8%)	555
Ahmed 2012 [20]	Zaria, Nigeria	57 (9%)	578
Sawe 2016 [21]	Eldoret, Kenya	4 (7%)	58

Table 3.3 Male-female breast cancer incidence in North Africa

Author	Location	MBC (%)	FBC
EL-Gazayerli 1963 [22]	Alexandria, Egypt	15 (6.8%)	204
Gebremedhin 1998 [24]	Addis Ababa, Ethiopia	10 (13.8%)	62
El-Omari-Alaoui 2002 [26]	Rabat, Morocco	71 (0.94%)	7482
Maalej 2008 [27]	Tunis, Tunisia	29 (2%)	1408
El-Habbash 2009 [28]	Tripoli, Libya	22 (1.4%)	1546
El-Shafiey 2011 [25]	Cairo, Egypt	32 (0.89%)	3564

Jewish ancestry does constitute a significant risk factor for MBC. Steinitz et al. compared 187 cases reported to the Israel Cancer Registry with 194 in the U.S. Third National Cancer Survey together with contemporaneous FBC rates [29]. In both countries MBC rates were related to those of FBC and the rate of MBC in Israel was higher than in the USA. When Mabuchi et al. carried out a case-control study of 52 MBC with 52 controls in 5 US cities, they found a significantly increased risk of cases being Jewish [30].

Following the isolation of the breast cancer susceptibility gene *BRCA2*, Couch et al. analysed 50 MBC cases and found pathogenic mutations in 7 (14%), of whom 4 were of Ashkenazi Jewish origin [31]. Brenner et al. studied 131 Israeli MBC cases and reported that there was an overrepresentation of Ashkenazi compared with Sephardic Jews with an almost doubling of risk [32]. As part of a large series of 10,000 cases, Frank et al. looked for mutations in 76 MBC cases and found them present in 21 (28%) of whom 11 39%) were Ashkenazim [33].

Sociodemographic Status

It can be difficult to precisely allocate individuals into a social class and proxy approaches have been adopted including years of education and job title. Nevertheless, a consistent effect of sociodemographic status (SES) on risk can be seen. In a relatively small case control study of 21 cases and 82 controls D'Avanzo & La Vecchia reported that there was a significant relation between years of education and risk [34]. Compared with men who had <7 years of education, those who had studied for ≥12 years had an odds ratio of 2.6. There was a threefold increase in risk for men of high versus low social class.

Using a 1% sample of all the US deaths in 1986, Cocco et al. compared 178 MBC with 1042 age matched controls and determined socioeconomic status based on longest held occupation [35]. There was a significant association of increased risk with SES with odds ratios of 1, 1.5 and 2.3 in low, medium and high categories respectively.

Hansen investigated members of the Danish National Pension Fund and identified 230 MBC cases [36]. For each, 56 controls of similar age were selected and among the variables studied were exposure to vehicle fuel and fumes together with social class. The latter was derived from job title with definitions from the Danish Institute of Social Sciences: Group 1 corporate managers and academics, Group 2 proprietors and small business managers, Group 3 nurses and technicians, Group 4 skilled workers, Group 5 unskilled workers. There was a higher but not statistically significant increase in risk for groups 1 and 2 compared with group 5.

Klinefelter's Syndrome

Individuals with Klinefelter's syndrome (KS), comprise 1 in 1000 of newborn boys. They have at least one X chromosome added to the normal XY karyotype (most frequently 47XXY). This is associated with testicular dysgenesis, aspermia,

gynaecomastia, and a variety of psychological disturbances. Wang et al. analysed the endocrine profile of 19 KS patients [37]. Plasma secretion rates of total and free testosterone were low, plasma estradiol, LH and FSH levels were elevated and there was increased peripheral conversion of testosterone to estradiol. In contrast, secretion and binding of estradiol was normal. Fluctuations in blood levels of LH, FSH, testosterone and estradiol were less marked than in healthy men.

In 1971 Harnden et al. who had collected 150 MBC cases from Birmingham and Edinburgh reported that 5 (3.3%) were chromatin positive [38]. Hultborn et al. studied 93 unselected MBC patients from the western Sweden and used fluorescence in situ hybridisation (FISH) on intact nuclei lymph nodes and reported a 7.5% prevalence rate of KS in MBC [39]. This suggested that there was a 50-fold increased risk in KS compared with XY males. Median age at diagnosis was 72 years in both groups of patients.

Others conducted follow-up studies of known cases of KS. Price et al. reported mortality data of a cohort of 466 KS followed for 25 years [40]. There were 2 fatal cases of MBC which represented a significant increase in risk, similar to that in the female population. From the Danish Cytogenetic Register Hasle et al. collected a cohort of 696 KS cases in which 39 cancers were diagnosed but no breast cancers [41]. Swerdlow et al. reported 163 deaths in a cohort of 646 KS patients with an RR of 1.63 (1.40–1.91) [42]. This was predominantly due to diabetes and vascular disease but there was however an increased risk of lung and breast cancer in patients with KS. In a large UK cohort comprising 3518 men with KS incidence and mortality were compared with that of men in the national population [43]. The standardised mortality ratio (SMR) for all cancers was 1.2. There was a higher mortality rate for lung cancer (SMR 1.5) and for MBC (SMR 57.80. Among those with 47XXY mosaicism the SMR was 222.8. In contrast there was a reduced risk of prostate cancer (SMR 0).

Gynaecomastia

The relationship between gynaecomastia and MBC remains problematic, in part because of the difficulty defining gynaecomastia. It means male breast enlargement but the majority of cases have enlargement because of increased subcutaneous fat (pseudogynaecomastia) rather than an increase in the glandular issue of the breast. Cakan & Kamat defined gynaecomastia in boys as being glandular tissue >5mm [44]. In contrast Daniels & Layer, reporting a series of 175 males >16 years with gynaecomastia had a threshold of 20 mm for making the diagnosis [45]. Such measurements are largely lacking in the epidemiological literature.

Simon et al. classified gynaecomastia based on size and described three grades [46]. Grade 1 is visible breast enlargement without redundant skin. Grade 2A is moderate breast enlargement but no skin redundancy and grade 2B moderate enlargement with minor redundant skin. Grade 3 gynaecomastia was defined as gross enlargement with skin redundancy and breast ptosis. Again, this classification has not been used epidemiologically.

Sirtori & Veronesi reported 218 cases of gynaecomastia of whom 108 had a biopsy [47]. No histological abnormality was found in 47 (44%) suggesting that these were pseudogynaecomastia cases. Among the true cases, the most obvious change was in the stroma with increased cellularity and hyalinisation in the fibrous component and a change in the loose periductal connective tissue to the mantle firm found in the female breast. There were variations in the proportion of the two components and sometimes fibrosis was total with adjacent ducts resting thereupon. Cysts were present in 105 (97%) of specimens but lobule formation was seen in only one case. The ductal tissue showed both atrophy and of proliferation with elongation and occasional twisting. Ducts comprised either two or three layers with marked proliferation in the basal layer. Mitotic activity was observed in 89 (82%) sometimes giving rise to true papillomas.

Gynaecomastia is common and shows temporal changes in incidence. It is found in up to 90% of neonates as a result of transplacental transfer of steroid hormones. This may persist for several months. There is another peak at puberty and up to 60% of 14-year old boys have gynaecomastia possibly because of relative delay in full testosterone synthesis or a temporary surge in aromatase activity, or variation in estrogen sensitivity. With increasing age and decreasing free testosterone there is another increase in incidence, correlated with body mass index, so that in autopsy studies up to 50% of the males had gynaecomastia [48]. Apart from the effects of aging and obesity, multiple diseases have been implicated including hyperthyroidism, liver disease, Klinefelter's syndrome and tumours of the testis and adrenal gland. Individuals who have starved and then refeed are also at risk, as are those undergoing chemotherapy, suffering from HIV and men with chronic illness.

In addition to this age-related increase in incidence of gynaecomastia the situation is exacerbated by the pharmacological interventions to which the aging body is prone. Many of the reports were anecdotal, so Deepinder & Braunstein carried out an assessment of the quality of the evidence, assigning a good, fair or poor score to each of the publications [49]. What emerged was that most of the reported associations were derived from poor quality evidence. Those drugs that were definitely associated with gynecomastia are summarised in Table 3.4. Approximately 10% of patients treated with spironolactone develop gynaecomastia and up to one in five of men given cimetidine have this problem.

Table 3.4 Drugs and gynaecomastia [49]

Definitely associated	Probably associated
Spironolactone	Risperidone
Cimetidine	Verapamil
Ketoconazole	Nifedipine
Human growth hormone	Omeprazole
Estrogen	Alkylating agents
Human chorionic gonadotrophin	HIV medications
Anti-androgens	Anabolic steroids
GnRH analogues	Alcohol
5-α reductase inhibitors	Opioids

In a Scandinavian study of risk factors for MBC, Ewertz et al. collected 282 cases from Denmark, Norway and Sweden between 1987 and 1991 [50]. They used self-questionnaires on 156 MBC cases who agreed to participate and with 468 male controls matched for country and year of birth. Significant risk factors that emerged included family history (OR 3.3), obesity, BMI > 30 (OR = 2.1), and diabetes (OR = 2.6). They asked in detail about gynaecomastia and found that many cases confused signs of breast cancer with gynaecomastia and suggested that this might explain the strong association previously reported.

Because gynaecomastia may be associated with absolute or relative estrogen excess Olsson et al. followed a cohort of 446 affected men to determine whether this was associated with increased risk of malignancy [51]. All had histologically confirmed gynaecomastia. Before being diagnosed with gynaecomastia, eight had prostate carcinoma, two unilateral MBC and one Hodgkin's disease. There was a total of 8375.2 person years of follow-up and during this time 68 cancers were diagnosed compared with an expected 66.07 (SIR = 1.03 (95% CI 0.80–1.30). There was a significantly increased risk of testicular cancer; SIR = 5.82 (95% CI 1.20–17.00) and squamous cell carcinoma of the skin; SIR = 3.21 (95% CI 1.71–5.48). No new cases of MBC were diagnosed but the diagnostic surgery may have substantially reduced this risk.

Satram-Hoang et al. conducted a pilot case-control study with 44 MBC and 77 age- and ethnicity-matched controls. Subset of the male breast cancer cases (n = 44) and age- and ethnicity-matched controls (n = 77) [52]. Of the MBC cases, 20% were overweight/obese with comorbidity present in 55%.There was a significantly greater proportion of MBC with gynaecomastia, family history of cancer, antibiotic use and smoking compared with the controls. The authors conceded that the study was underpowered and a large collaborative effort was needed.

That was provided by Brinton et al. who accessed 26 million hospital discharge records from the US Veterans Administration covering 1969 to 1996 and determined the relationship between confirmed medical conditions and risk of subsequent MBC [53]. There were 4,501,578 males aged between 18 and 100 years, and among these 642 MBC cases were diagnosed. The relative risk of various medical conditions are summarised in Table 3.5 which shows that gynaecomastia and Klinefelter's syndrome were associated with the highest relative risks. Other conditions that had been previously reported to increase risk of MBC such as thyroid diseases, smoking-related conditions, liver cirrhosis, prostatic hyperplasia, and fractures did not affect risk in this study. Although the link with diabetes disappeared after adjust-

Table 3.5 Pre-existing medical conditions and risk of MBC [53]

Condition	Relative risk	95% confidence interval
Diabetes	1.30	1.05–1.60
Obesity	1.98	1.55–2.54
Orchitis/epididymitis	1.84	1.10–3.08
Klinefelter syndrome	29.64	12.26–71.68
Gynaecomastia	5.86	3.74–9,17

ment for obesity, that with gynaecomastia persisted. This risk was highest for those diagnosed with MBC in the following 2–5 years but was also evident in those diagnosed >5 years later. The problem remains concerning the lack of precision since these cases will have been a mixture of true and pseudo gynaecomastia. Prospective studies of radiologically or histologically defined cases are going to be necessary,

Various studies have shown a very different pattern of steroid receptor expression in gynaecomastia and MBC. Sasano et al. investigated ER, PR, and AR in 30 gynaecomastia specimens and 15 MBC samples [54]. All the MBC showed strong cytoplasmic staining for ER/PR compared with only 11/30 (37%) of gynaecomastia. There was however nuclear ER/PR expression in ductal cells of all the gynecomastia specimens. AR was present in 13/15 (87%) of MBC and all cases of gynecomastia. There was a significantly higher proportion of ER/PR/AR-positive cells in gynecomastia compared with MBC. Interestingly, there was a positive association between AR and ER/PR in gynecomastia but a significant inverse association in MBC. Increased aromatase expression in the stromal cells is considered to contribute to the increased in situ estrogen concentration and the development of male breast carcinoma.

Ferreira et al. measured prolactin receptor (PRLR) expression in 30 gynaecomastia and 30 MBC specimens [55]. Additionally they determined ER, PR and AR status and male breast carcinoma (MBC). There was PRLR positivity in 20% of the gynaecomastia cases and in 60% of MBC specimens. The PRLR staining was mostly in luminal cell borders of gynaecomastia whereas it was heterogeneous and predominantly cytoplasmic in the MBC. The quantitative and qualitative differences in PRLR expression in gynaecomastia and MBC also suggests that the former is not necessarily a forerunner of the latter.

Kornegoor et al. examined tissue microarrays from 46 gynaecomastia specimens using IHC for a range of epitopes including ER, PR, HER2, AR, CK5, CK14, cyclin D1, and Bcl-2 [56]. They found a consistent IHC staining pattern of one myoepithelial and two epithelial cell layers with a distinctive immunohistochemical staining pattern. There were vertically oriented cuboidal/columnar cells in the intermediate luminal layer which were ER/PR +ve and expressed Bcl-2 and cyclin D1. The cells of the inner luminal layer were smaller, usually ER/PR−ve, Bcl-2−ve, CK5+ve and often CK14+ve. In contrast, in the DCIS cases that they examined the cells were ER+ve and CK5/CK14 −ve. This suggests that there are different cell compartments in gynaecomastia so that it might not be an obligate precursor of MBC.

Testicular Malfunction

There is a substantial body of evidence that subnormal testicular function is an important risk factor for MBC. In 1963 Schottenfeld et al. published the first case-control study with 53 MBC cases who were interviewed and two control

groups with gynaecomastia (126) or colon cancer (154), matched for age, time of diagnosis and who had been treated in the same hospital as each MBC case [57]. Participants were asked among many questions whether they had had mumps and the age at which this had happened. Four of the cases reported mumps and three of them were diagnosed post-puberty. One of the gynaecomastia controls reported mumps but none of the colon cancer controls had been affected.

Keller collected 181 MBC cases from Veterans Administration Hospitals and by random dialling of other veterans selected two groups of controls matched for age and location, with one group having a non-malignant diagnosis (181) and the other comprising males with bladder or renal cancer (181) [58]. Of the cases, 19 (11%) had a clinical diagnosis of atrophic, enlarged or inflamed testes compared with 22 (12%) of the cancer controls. Nicolis et al. reported a case of MBC who had mumps orchitis at age 16 and was subsequently found to have aspermia [59]. At the age of the age of 41 he developed type II diabetes and was diagnosed with MBC aged 47.

In Mabuchi's study there were 52 MBC cases and 52 controls, matched for age, ethnicity and marital status [30]. They reported a significant association of MBC with mumps diagnosed at age ≥20 years, Of the cases, seven had been employed in hot environments – steel mills, blast furnaces and rolling mills whereas none of the controls had worked at such sites. Casagrande et al. compared 75 non-Hispanic white MBC patients with 69 neighbourhood controls aged within 5 years of each case. In both groups 3 men had been diagnosed with mumps at age ≥20 years [60]. Undescended testis was reported by three cases and one control.

Olsson & Ranstam reported that testicular damage was reported by 6/95 (6%) of MBC cases compared with 3/383 (1%) lung cancer controls and 2/69 (3%) non-Hodgkins lymphoma controls [61]. In a Franco-Swiss collaboration, 91 MBC cases were compared with 255 cancer controls matched for age and year of diagnosis [62]. Of the controls, 91 had colon cancer. 91 haematological malignancy and 73 had basal cell carcinoma. Working in a hot environment was reported by 5 (5%) cases and 5 (2%) of the controls.

Thomas et al. conducted standardised personal interviews of 227 MBC cases and 300 age-matched controls selected by controls by random digit dialling for those aged <65 and Insurance records of older men [63]. There was no excess of mumps in the cases 6 (3%) versus 10 (3%). Nevertheless, undescended testis was reported by seven cases and one control giving a significantly elevated relative risk of 11.6. Additionally, more of the cases had prior inguinal herniorraphy, orchidectomy and testicular injury. In a relatively small study of 21 MBC cases and 82 hospital controls, D'Avanzo reported the relative infertility of the cases [34]. Of the controls 25 (31%) had no children compared with 15 (67%) of the MBC cases. In another small study from Athens,

Table 3.6 Case control studies of testicular damage and risk of MBC

Author	Feature	MBC	Affected	Controls	Affected
Schottenfeld 1963 [57]	Mumps	53	4	154/127	0/1
Keller 1967 [58]	Clinical	181	19	181	22
Mabuchi 1985 [30]	Mumps ≥20 years	52	7	52	1
Casagrande 1988 [60]	Mumps ≥20 years	75	3	69	3
Olsson 1988 [61]	Testis damage	95	6	383/69	3/2
Lenfant-Pejovic 1990 [62]	.High temp	91	5	383	5
Thomas 1992 [63]	Undesc testis	227	7	300	1
D'Avanzo 1995 [34]	No children	21	15	82	25
Petridou 2000 [64]	High temp	23	6	76	22

Table 3.7 Collaborative studies of testicular damage and MBC risk

Study	MBC cases	Orchitis	Cryptorchidism	No children
VA [53]	643	RR = 1.3*		
MBCPP [65]	2405	OR 1.43	OR 2.18	OR 1.29*

VA Veterans Administration, *MBCPP* Male Breast cancer Pooling Project, *RR* relative risk, *OR* Odds ratio
*Statistically significant

Petridou et al. reported a high ambient working temperature in 6/23 (26%) of cases compare with 22/76 (29%) of controls (Table 3.6) [64].

The recognition that small studies had inadequate statistical power prompted collaborative research with cohort studies which yielded more definitive results. Brinton et al. from the National Cancer Institute examined the U.S. Veterans Affairs database of 26 million discharge records between 1969 and 1996 [53]. They found 643 MBC cases diagnosed >1 year after discharge out of 4,501,578 veterans and were able to make adjustment for age, ethnicity, year of diagnosis, length of follow-up, and number of consultations. A past history of orchitis or epididymitis was associated with a significant increase in relative risk of MBC (RR =1.30, 95% CI 1.05–1.60) (Table 3.7).

The Male Breast Cancer Pooling Project analysed data from 11 case–control and 10 cohort studies [65]. There were 2405 MBC cases with 1190 in case–control and 1215 from cohort studies with 52,013 controls. For individuals with cryptorchidism the odds ratio was elevated but without statistical significance (OR = 2.18; 95% CI = 0.96 to 4.94) and the same was true for orchitis (OR = 1.43; 95% CI = 1.02 to 1.99). For those who had never fathered children there was a significant increase in risk (OR = 1.29; 95% CI = 1.01 to 1.66).

Although there are variations in the findings, the majority of studies do suggest that testicular damage, whether traumatic, viral, vascular or ambient temperature-related does lead to an increased risk of MBC. There is the possibility that testosterone replacement in high risk cases might improve quality of life and possibly reduce the likelihood of development of MBC.

Transsexuality

In 1968, Symmers described 2 unfortunate cases of birth males who had undergone gender realignment and taken estrogens, oral contraceptives and implants to promote breast enlargement [66]. They both led a demimondaine existence and developed MBC at the age of 30, having been taking estrogens for 5 years. Sadly both succumbed rapidly to aggressive disease. Kanhai et al. investigated the histological changes in 14 castrated males receiving estrogens and compared these with alterations in two men taking antiandrogens for prostate cancer [67]. In the latter group they reported some development of acini and lobules. Among the transsexuals given progestins and estrogens they observed full development of acini/lobules with pseudolactational changes. This suggests that a combination of progestin and estrogen are required to mimic normal female breast morphology in the male.

There have now been several other reports linking estrogen therapy with MBC in transsexuals and these are summarised in Table 3.8 [66, 68–75]. It is striking that these cancers occurred in relatively young individuals with the oldest case of invasive cancer being 58. All tumours were invasive ductal cancers (IDC) and there was a disproportionately large number of ER−ve carcinomas (50%). When Gooren et al. reported follow-up of a cohort of 2307 male to female transsexuals in 2013 there was only one case of MBC and they concluded that cross-sex hormone administration did not increase the risk of breast cancer development. By 2015 they had observed two further cases of what was a relatively rare complication of administering estrogens to males.

In 2003, Moore et al. from Johns Hopkins reviewed the recommendations from six specialised gender realignment centres for systemic pre-surgical therapy in

Table 3.8 MBC developing in male to females taking estrogens

Author	Age at diagnosis	Histology	Estrogen therapy	Tumour ER status
Symmers 1968 [66]	30 30	IDC IDC	Pellets OC	? ?
Pritchard 1988 [68]	45	IDC	Premarin	ER−ve, PR+ve
Ganly 1995 [69]	50	IDC	Premarin	ER−
Grabellus 2005 [70]	46	IDC	>20 years ? type	ER−, PR−ve
Dhand 2010 [71]	58	IDC	>11 years ? type	ER+. PR+ve
Gooren 2013 [72]	45	IDC	36 years ? type	ER+ve. PR−ve
Pattison 2013 [73]	43	IDC	Premarin	ER−ve. PR−ve
Maglione 2014 [74]	55 65	IDC DCIS	Premarin Premarin	ER−ve, PR−ve ER+ve, PR+ve
Gooren 2015 [75]	52 46	IDC	EE Cyp E2 patch	ER+ve, PR−ve ER+ve. PR+ve

OC oral contraceptive, *EE* ethinylestradiol, *Cyp* cyproterone acetate, *E2* estradiol, *Premarin* conjugated estrogens

males wanting a female phenotype [76]. Most were giving ethinylestradiol 50–100 μg daily and cyproterone acetate 100 mg or conjugated equine estrogens 0.625 10 mg/day. In 2009 Hembree et al. reported the Endocrine Society's Practice Guidelines for treatment of transsexuals. These were as follows:

- Regular clinical and biochemical follow-up
- Evaluation for cardiovascular risk factors
- Those with no known risk factors for breast cancer to follow female screening guidelines
- Follow prostate screening advice for biological men

Prostate Cancer

In 1986 a review of 19 cases of MBC reported two patients who had been taking estrogens for 12 years to treat prostatic carcinoma [77]. In 2004 Coard described bilateral breast cancers in a male who had taken long-term estrogen therapy for carcinoma of the prostate [78]. Karamanakos et al. diagnosed MBC in an 82 year old who had received the 5-α reductase inhibitor (5ARI) flutamide for >8 years [79]. To investigate this association, Bird et al. used data from a health insurance company to design a case control study with 339 MBC patients and 6780 age-matched controls [80]. They found no significant association between use of flutamide or dutasteride and risk of MBC even after >3 years of exposure.

5-ARIs are widely used to treat men with symptomatic benign prostatic hyperplasia and so there was concern about possible cancer risk in a population with a non-malignant disease. Duijnhoven et al. conducted another case-control study using data from the United Kingdom Clinical Practice Research Datalink database [81]. There were 3398 MBC cases who were compared with 3930 age-matched controls. For those who had ever used 5-ARIs the breast cancer odds ratio was 1.08 compared with non-users. There was no increased risk after short- or long-term treatment.

Modifiable Factors

Smoking

There is an enigmatic relationship between smoking and breast cancer. In females smoking has an anti-oestrogenic effect in that it reduces premenopausal urinary oestrogens [82], increases postmenopausal androgens [83], leads to an earlier menopause [84], which while protecting against endometrial cancer [85] but increasing risk of osteoporosis [86]. Theoretically this addiction could protect against breast cancer but an overview of studies of smoking and risk of FBC has shown a neutral effect [87]. Hsing et al. interviewed next-of-kin of 178 men who died of MBC and also those of 512 males who had died of other causes [88]. Among the information

sought was smoking history and alcohol consumption but no association was found for either factor.

Based on 23 cases of histologically confirmed MBC and 76 age-matched controls from greater Athens, Petridou et al. investigated the impact of smoking on risk. Among the cases there were 3 current smokers compared with 31 of the controls (OR = 0.22 P = 0.03). This indicated a possible protective effect. In contrast,in a cohort study of 324,920 males reported by Brinton et al., in which 121 MBC were diagnosed, there was no clear relationship between smoking and risk nor any dose response identified [89]. The largest reported study is the Male Breast Cancer Pooling Project consortium which included 2,378 cases and 51,959 controls derived from 10 cohort and 10 case-control studies [65]. The authors reported that there was no association between risk of MBC and smoking status, duration or age at commencement. With the statistical power of this meta-analysis it can be stated with some confidence that smoking is not an important aetiological factor in the development of MBC.

Alcohol

There have been conflicting results and opinions concerning the relationship between alcohol consumption and risk of MBC. Yet again this illustrates the pitfalls of extrapolating from relatively small data-sets. Sorensen et al. analyse risk of malignancy in 11,605 Danish patients with cirrhosis who survived for >1 year [90]. FBC developed in 81 and MBC in 2 giving a M/F ratio of 0.024, suggesting a possible increase in risk for MBC. Guenel et al. conducted case-control study derived from 5 countries Denmark, France, Germany, Italy, and Sweden with 74 MBC cases and 1432 age and location-matched controls [91]. Compared with controls, MBC risk increased by 16% for each 10 g alcohol/day ($p < 0.001$). Consuming >90 g/day, compared with an intake of <15 g, gave an odds ratio of 5.89.

In another Scandinavian study of 58 MBC treated in Helsinki, Liuekkonen et al. reported that of those with known risk factors 43% had a high alcohol intake compared with 20% of the Finnish male population [92]. Additionally, 4 (7%) had developed cirrhosis but the authors cautioned that the proportion with recorded risk factors was only 41%. The situation was clarified by Brinton et al. in a prospective study of 324,920 men, including 121 developed breast cancer [83]. Although other risk factors were confirmed there was no association between alcohol intake and risk.

Weight

In a study of 75 MBC cases and matched neighbourhood controls, Casagrande et al. examined a variety of clinical and endocrine variables but found that the only significant association was weight at age 30 [60]. There was a doubling of risk for men weighing ≥80 kg at that age compared with those who weighed <60 kg. In a smaller Italian study with 21 cases and 82 controls, D'Avanzo & La Vecchia reported that

cases were heavier than controls but after adjusting for height this diminished and no association with body mass index (BMI) was found [34].

As an alternative approach, Hsing et al. analysed data from the 1986 US National Mortality Followback Survey (NMFS) [82]. They identified 178 men who died from breast cancer and conducted next-of-kin interviews together with those of 512 male controls dying of other causes. There was an increased risk of MBC in those deemed as very overweight by their next-of-kin (odds ratio = 2.3). When divided into quartiles of BMI, compared with the lowest quartile the relative risks were 1.3, 1.6, and 2.3, showing a significant dose-response relationship.

A Canadian study with 81 cases and 1905 male controls reported a doubling of risk (OR 2.16) for those weighing ≥90 kg compared with men <73 kg Johnson et al. [93]. Taller men were also at increased risk OR 1.57 for those >180 cm compared with <172 cm. There was a significant correlation between increasing BMI and higher risk with an odds ratio of 1.63 for those with a BMI ≥29 kg/m^2. The NIH AARP Diet and Health study also confirmed that obesity was significantly linked to risk with a relative risk of 1.79 for those with a BMI ≥30 compared with <25 kg/m^2 [65].

Diet

Research on diet and risk of FBC has been bedevilled by problems such as different recall of diet in case control studies, underpowered investigations on individuals with a narrow range of consumption of foodstuffs and difficulties in accurately determining intake. These obstacles are amplified in MBC so that results are contradictory or inconclusive. Hsing et al. carried out a case-control study based on information from next-of-kin interviews of 178 men who died of breast cancer compared with 512 male controls dying from other diseases [81]. Apart from demography, information was sought concerning diet, exercise, occupation, height and weight, and use of tobacco and alcohol. They reported that red meat consumption was associated with an increased risk of MBC whereas consumption of vegetables and fruit led to a decreased risk, albeit with non-significant trends

Rosenblatt et al. compared 220 MBC cases from 10 cancer registries with 291 controls collected by random digit dialling together with men aged ≥65 from Medicare beneficiary lists [94]. They reported that there were no trends in risk associated with increased consumption of particular lipids, protein, fibre, carbohydrates, or vitamins except ascorbic acid consumption which increased risk. They concluded that diet was not a major determinant of MBC risk.

Occupation

In 1985 Mabuchi et al. conducted a small study with 51 cases and a similar number of controls and reported an increase in risk among men who had worked in a high environmental temperature such as blast furnaces and steel mills [30]

Table 3.9 MBC risk and occupation [35]

Occupation	Cases	Controls	Odds ratio	95%CI
Blast furnace	6	11	3.4	1.1–10.1
Motor vehicles	7	16	3.1	1.2–8.2
Sawmills	3	5	4	0.9–17.4
Restaurant/bar	7	18	2.2	0.9–5.4
Grocery	4	5	4	0.9–17.7

(Table 3.9). Following this McLaughlin et al. determined the employment history of 333 Swedish men with MBC [95]. The highest standardised incidence ratio was observed in those working in the soap and perfume industries (SIR = 7.6), followed by retail hardware (4.2) and newspaper printing (3.9). For specific industries there was an increased risk for iron and steel workers (SIR 2.6) together with agriculture (2.8) and brewing (2.8).

Robinson et al. investigated a cohort of 27,362 members of the U.S. Carpenters' Union who had died between 1987 and 1990 [96]. Age-adjusted proportionate cancer mortality ratios (PCMRs) were calculated and among white carpenters in industrial wood products there was significantly raised mortality occurred for MBC (PCMR = 469, CI = 128, 720). Additionally there was an excess breast cancer risk for men in wood machining trades. The authors concluded that construction carpentry was an extremely hazardous occupation.

In the 1% sample of all the US deaths in 1986, Cocco et al. reported odds ratios for occupations with at least 3 exposed cases and their major findings are summarised in Table 3.9 [35]. The only significantly elevated SIRs were found among workers in sawmills and blast furnaces, confirming the findings of Mabuchi et al. [30] and Robinson et al. [90].

Using the Danish Cancer Registry Hanson identified 230 MBC and from the National Pension Fund identified 56 controls for each together with employment history [36]. For those who were <40 years when first exposed occupationally to fuel and combustion products there was a significantly increased risk of MBC (OR 3.7). When corrected for a 10-year lag time the OR rose significantly to 5.4.

After identifying pathogenic BRCA1/2 mutations in a group of Italian MBC patients: Palli et al. carried out a case-case study to determine whether there was a link between carrier status and occupation using a case-case design [97]. They calculated case-only odds ratios (CORs) and reported that the most frequent occupation was truck-driving with 3/4 BRCA-related cases and 2/19 unrelated cases. When cases were categorised as to whether they had or had not been a truck-driver the COR was 25.5 suggesting that mutation carriers were at increased risk of MBC if exposed to polycyclic aromatic hydrocarbons.

Professional firefighters are another workgroup over-exposed to polycyclic aromatic hydrocarbons as well as other toxins. Ma et al. examined mortality rates in 34,796 male and 2017 female Florida firefighters [98]. Among the men there was no overall excess cancer mortality but there were significantly more MBC deaths (SMR 7.41).

Ionising Radiation

Occupational radiation exposure leading to cancer may render affected individuals eligible for state compensation. This is true for certain forms of FBC and consideration is currently being given to include MBC so this has potential economic consequences. In the early twentieth century there was a fashion for irradiation of both gynaecomastia and enlarged thymus glands in infants. Lowell et al. reported that a 10-year old boy with gynaecomastia was irradiated in 1932 and was diagnosed with MBC at the age of 46 [99]. Greene et al. described a case of MBC occurring in a cytogenetically normal man 30 years after receiving thymic irradiation [100]. In a large case-control study of 2856 irradiated and 5053 non-irradiated siblings followed from 1953 there was a significantly elevated risk of cancer in the irradiated group [101]. This was particularly the case for skin and breast cancers but only in females.

Thomas et al. conducted a population-based case-control study of MBC risk in relation to radiation exposure using 227 cases and 300 controls [102]. The study suggested that ionizing radiation can cause MBC in that there was a modest association of increasing risk with greater number of chest X-rays. Furthermore there was an increase in risk in men who had irradiation of the chest and adjacent body areas. This risk appeared from 20 to 35 years after exposure and declined thereafter. The authors suggested that there was a similar sensitivity of prepubertal breast tissue in both males and females.

Ron et al. examined MBC incidence among 45,880 Japanese atomic bomb survivors using the Hiroshima and Nagasaki Tumour Registries [103]. There were nine MBC among exposed individuals (1.8 per 100,000 person-years), and three in the non-exposed cohort members (0.5 per 100,000 person-years). Confirmatory data was reported in 2016 by Little et al. who compared radiation-associated excess relative and absolute risks of MBC and FBC in atomic-bomb survivors, as shown in Table 3.10 [104]. There was a significant dose related excess of MBC. Although the absolute numbers of MBC were small there was a 15-fold increase in relative risk of MBC and a 5 fold increase in relative risk mortality from the disease. Nevertheless the findings need to be interpreted cautiously because of the small number of MBC cases.

Table 3.10 Incidence and mortality of breast cancer in atomic bomb survivors (Little 2016)

	Male	Female
Incidence		
N	32,411	47,769
Breast cancer cases	7	847
Rate (10^5/year)	0.9	64.9
Relative risk	15	1
Mortality		
N	35,687	50,926
Breast cancer deaths	6	324
Rate (10^5/year)	0.47	16.1
Relative risk	5	1

In the five series study the mortality rates in US military personnel participating in atomic weapons testing was reported by Till et al. [105]. This suggested that atomic veterans had a non-statistically significant 39% increased risk of MBC.

Jartti et al. followed a cohort of 1312 Finnish doctors with accurate data from the occupational radiation exposure registry acquired from 1970 to 2001 and compared their cancer incidence with that of 15,821 doctors who had never been monitored [106]. Cases were identified by linkage to the Finnish Cancer Registry. The cumulative radiation dose exceeded 0.3–3.0 mSv during a trimester for 1029 (60%) of the exposed group with 6% of radiologists receiving a cumulative dose of ≥50 mSv. There were 41 cancers in the radiation-exposed and 998 in the never-monitored group. Standardized incidence ratios (SIR) for all cancers were similar to those of the general population, among physicians monitored for radiation [SIR 1.0, 95% confidence interval. There was a slightly elevated risk of FBC found among monitored physicians compared with non-monitored. It was concluded that medical radiation is not a strong risk factor for cancer among doctors and a possible excess risk could not be reliably demonstrated after up to 30 years of follow-up.

Therapeutic total body irradiation (TBI) with bone marrow transplant has been very successfully used in the treatment of childhood malignancy. The Late Effects Study Group reported follow-up of cohort of 1,380 children treated for Hodgkin's disease (HD) between 1955 and 1986 [107]. The median age at diagnosis was 11.7 years with a follow-up of 17 years. There was a total of 212 new cancers giving a standardized incidence ratio [SIR] of 18.5, (95% CI 15.6, 21.7). The commonest second cancer site was the breast (SIR, 56.7) and of the 30 breast cancer cases one (3%) was male. Latz et al. reported a 29-year-old MBC case diagnosed 13 years after total body irradiation (TBI) and bone marrow transplantation (BMT) for acute lymphoblastic leukaemia (ALL) [108]. The patient relapsed and died 17 months after mastectomy and PMRT. Details are given in Table 3.11.

Lowe et al. treated a 34-year-old man with stage IIB node-positive breast cancer who had been treated by TBI and BMT for ALL at age 19 [109]. Ninkovic et al. recorded a male with invasive lobular carcinoma which had developed 14 years after diagnosis with nodular sclerosing HD [110]. This had been treated with ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) and radiotherapy. The tumour was T2N0M0 and ER+ve, PR±, HER2−ve. In this case, after a modified radical mastectomy, adjuvant fluorouracil, adriamycin cyclophosphamide (FAC), PMRT and tamoxifen the patient was alive without recurrence 2 years later. The case of MBC reported by Alazhri et al. was aged 23 having been treated by TBI and BMT

Table 3.11 MBC development after total body irradiation

Author	Age at TBI	RT Dose	Interval	Receptors
Latz 2004 [101]	16	12Gy	13 years	ER+ve, PR+ve HER2?
Lowe 2008 [102]	19	13.2Gy	15 years	ER+ve, PR+ve, HER2+ve
Ninkovic 2012 [103]	42	?	14 years	ER+ve, PR±, HER2−ve
Alazhri 2016 [104]	4	?	19 years	ER+ve, PR+ve, HER2+ve

at the age of 4 [111]. The interval of 19 years was the longest so far recorded, suggesting the need for long-term surveillance of those with HD and ALL treated by TBI in childhood.

In 1945 the secret city of Ozyorsk was created in the Southern Urals as the USSR's largest facility for the production of nuclear weapons. Workers were exposed to high levels of ionising radiation in the early years with risk from inhalation of plutonium aerosols. Deltour et al. examined death registry data to determine mortality rates from 1998 to 2010, together with time trends in age-standardised mortality rates between 1953 and 2010 of workers of the three main plants compared with the other Ozyorsk residents [112]. They reported that for men there was a lower overall cancer rate among workers compared with national figures (0.86) and there were no reported cases of MBC. The data are heterogeneous but the overall impression is of an increase in relative risk of MBC after radiation exposure but because of the relatively small numbers of cases the effect is small in population terms.

Electromagnetic Fields EMF

In 1987 Richard Stevens put forward the hypothesis that use of electrical power and resulting electromagnetic fields (EMF) was associated with the increase in risk of breast cancer [113]. This was based experimental evidence from rodent models exposed to a chronic magnetic field (60 Hz) which inhibited melatonin production and increased the extent of DMBA-induced mammary tumours. He freely admitted that there was no human evidence of such an effect but this could be obtained from epidemiological studies. The first reported was that of Demers et al. who conducted a case control study in males based on job title and reported an odds ratio (OR) of 1.8 for MBC for those in occupations associated with high EMF exposure (Table 3.11) [114].

There have now been 7 case-control and 11 cohort studies which have attempted to determine whether such an increase in risk is real and these were combined in a meta-analysis performed by Sun et al. [115]. The outline results are summarised in Table 3.12 [35, 109, 114, 116–131]. For the majority of studies exposure to EMF was based on job title and in only seven was there some attempt to quantify exposure. For the case-control studies the OR was 1.39 (95% CI 0.95. 2.04 and for the cohort studies 1.31 (95% CI 1.12, 1.53). In the individual studies a statistically significant result was achieved in two cohort studies and one case control study. Overall these findings indicate the precariousness of trying to find an association between a largely unquantified potential risk factor and a rare malignancy.

Further light has been shed on EMF and MBC risk by a large Canadian case-control study in which participants' lifetime EMF exposure was ascertained blindly by experts, based on occupational histories [132]. There were 115 MBC cases and 517 controls and participant exposure was categorised as <0.3, <0.6 and ≥0.6 Tesla. For men with an exposure of ≥0.6 compared with 0.3 Tesla the

Table 3.12 Meta-analysis of EMF exposure and MBC risk (Sun 2014) [115]

Author	Cases	Controls	Exposure	Risk
Case-control				
Demers 1991 [114]	33	59	Work	OR =1.8
Loomis 1992 [109]	3	33	Work	MOR = 2.2
Rosenbaum 1994 [110]	6	39	Work	OR = 0.6
Stenlund 1997 [111]	3	71	Measured	OR =1.5
Cocco 1998 [35]	9	63	Work	OR = 1.0
Feychting 1998 [112]	2	11	Measured	RR = 2.1
Park 2004 [113]	1	4	Power output	MRR = 1.09
Cohort				
Matanoski 1991 [114]	2	50,582	Measured	SIR = 6.5
Tynes 1992 [115]	12	37,945	Work	SIR = 2.07
Guenel 1993 [116]	2	1,401,967	Work	SIR = 1.36
Theriault 1994 [117]	7	223,292	Measured	SIR = 0.85
Floderus 1994 [118]	3	207,540	Measured	RR = 4.9
Savitz 1995 [119]	6	138,905	Measured	SMR = 0.8
Fear 1996 [120]	14	252,663	Work	SIR = 0.5
Johansen 1998 [121]	203	1,779,648	Work	RR = 1.31
Floderus 1999 [122]	2	25,135	Measured	RR = 1.2
Pollan 2001 [123]	203	1,779,646	Work	RR = 1.31
Nichols 2005 [124]	11	72,889	Work	SMR = 1.44

odds ratio for MBC was 2.77, indicating that this question requires further large scale investigation.

HIV

Sharma and Iyer described a case of Bowen's disease of the nipple in an HIV-positive male [133]. He gave a one year history of a scaly lesion on nipple for one year and biopsy confirmed squamous cell carcinoma in with no evidence of invasive carcinoma. He was treated by simple mastectomy and negative sentinel node biopsy.

Calabresi et al. reported a 65-year-old heterosexual man, with AIDS who was diagnosed with MBC 8 years later [134]. Past history included secondary syphilis and liver cirrhosis, resulting from hepatitis C. At the time of cancer diagnosis, he was receiving HAART with abacavir, lamivudine, unboosted atazanavir and had an undetectable HIV viral load. He was treated by mastectomy and axillary dissection for a grade 2 ductal carcinoma 1.2 cmd with 1/20 nodes. Surgery was followed with local radiotherapy and adjuvant tamoxifen. Although HIV infection can be associated with transient gynaecomastia [135] as can indinavir antiviral therapy [136], the minimal number of MBC cases suggest that HIV is not significantly associated with an increase in risk of the disease.

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Chapter 4
Genetics

Abstract Genetic studies have demonstrated multiple differences between male and female breast cancer, most noticeably that mutations of *BRCA1* play a very small role in MBC whereas those of *BRCA2* may be associated with up to 14% of male cases. Mutations of *PALB2*, partner and localiser of BRCA2, have been found in 16% of MBC cases, with or without a family history. In a large genome wide association study a common variant of *RAD51B,* a low penetrance gene, was found to be significantly associated with MBC. The EMSY gene is amplified in 13% of sporadic FBC but in 35% of MBC, with low amplification in *BRCA2* associated cancers. Mutations of androgen receptor gene and *CYP17* are rare in MBC. Bacterial artificial chromosome (BAC) arrays have revealed more genomic gains and fewer genomic losses in MBC, identifying 2 subgroups: male-complex and male-simple, the latter being found only in men. Genetic testing should be considered in men having one first degree relative with MBC and ≥1 with FBC or ovarian cancer since among this group, mutations have been found in 36%.

The great tragedy of Science – the slaying of a beautiful hypothesis by the ugly truth.
Thomas Huxley

Because of an appreciation of the need to collaborate in order to obtain meaningful information, geneticists have led the field in the study of MBC. As a result there is a great deal of knowledge on the subject but every new advance brings forth as many questions as answers. In 1975, 39 cases of MBC were reported from Yale New Haven Hospital and these included 2 brothers who were diagnosed aged 52 and 69 [1]. Of 142 MBC cases seen at the Memorial Sloan-Kettering Cancer Center and the Ochsner Clinic, 15% gave a family history of breast cancer but this had no impact on stage at diagnosis or prognosis [2]. From 10 population databases, 320 MBC were identified of whom 75% participated in a case control study with age-matched controls selected by random digit dialing [3]. Among the cases MBC was diagnosed in 3 fathers, 1 brother and 4 maternal uncles but in only one brother of a control. The odds ratio for any male with a relative with MBC was 6.07. In contrast having a relative with female breast cancer (FBC) was associated with an odds ratio of 2.17. In a Swedish study the incidence of cancer among first degree relatives of 153 MBC cases was determined and the standardised morbidity ratio (SMR) was elevated at 1.36 [4]. There were significantly elevated SMRs for FBC and ovarian cancer being 1.80 and 2.27 respectively.

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Table 4.1 Sex chromosome aneuploidy in MBC and controls (Jacobs 2015) [7]

% Aneuploidy		0	<2	2–4	5–9	10–19	≥20
<45 years	Cases	77%	4%	15%	4%	0	0
	Controls	62%	8%	31%	0	0	0
45–64 years	Cases	45%	15%	33%	5%	1%	0
	Controls	57%	0	24%	14%	5%	0
65–80 years	Cases	29%	12%	33%	11%	10%	5%
	Controls	15%	5%	45%	5%	5%	25%
Total	Cases	37%	13%	32%	8%	6%	3%
	Controls	43%	4%	33%	7%	4%	9%

Aneuploidy

Teixera et al. performed cytogenetic analysis of three cases of gynaecomastia and four MBC and found a normal karyotype in two gynecomastias but an abnormality in one who had a prior MBC excised [5]. In this small study there were clonal abnormalities in all 4 MBC cases, suggesting that gain of the chromosome X and 5, together with loss of 5 and Y together with del(18)(q21) were non-randomly present in MBC.

Using a multiplex ligation-dependent probe amplification method Lacle et al. investigated copy number changes on chromosome16q in 135 MBC tumours [6]. There were copy number changes present in 112 (83%). Two recurrent amplicons were found on 17q23.1 in 40% of MBCs compared with 60% of FBCs. This resulted in increased copy numbers of neurogenic differentiation factor 2 *NEUROD2*. There was a significant correlation between amplification of *NEUROD2* and grade of the tumour ($p < 0.0001$). *NEUROD2* copy number gain was associated with a significantly worse survival ($p = 0.015$).

In a large scale study of aneuploidy Jacobs et al. used X and Y centromere probes on blood smears from 565 MBC and 54 male controls [7]. The results in terms of proportion of aneuploidy and age of participants are summarised in Table 4.1. Aneuploidy was seen in 63% of the cases and 57% of the controls. There was a significant increase in proportion of aneuploid cells with age but this was more marked in the controls 85% versus 71%. The authors concluded that aneuploidy in MBC warranted further investigation in cohort studies.

BRCA1/2

In 1994 the identification and localisation of the two major breast cancer susceptibility genes was achieved [8, 9]. *BRCA1* is located on 17q21 and *BRCA2* on 13q12-13 with the former exerting a more major role in hereditary FBC. It therefore came as a surprise when Stratton et al. reported that in 22 families with at least one affected male there was no linkage between *BRCA1* and MBC [10]. Furthermore, in

an Icelandic extended pedigree study of 252 males and 229 females there were 4 cases of MBC and 3 of FBC and all had *BRCA2* associated cancers with loss of the wild-type allele [11]. Further work by the same group to include 21 families with 9 MBC cases revealed a deletion in exon 9 of *BRCA2* in all the cases, indicative of a founder effect [12].

The Cambridge Group analysed 94 British MBC cases looking for *BRCA1* and *BRCA2* mutations, and calculated breast cancer risk in female relatives using family history data [13]. Nineteen men (20%) had a first-degree relative with breast cancer and of these seven also had a second-degree relative with the disease indicating a 2.4 fold increase in risk of FBC compared with the general population. There were no *BRCA1* mutations but five men were *BRCA2* mutation carriers.

The Breast Cancer Linkage Consortium collected 164 families with breast/ovarian cancer and germline *BRCA2* mutations to evaluate genotype-phenotype correlations [14]. By the age of 80 years, the cumulative risk of breast cancer in male carriers of a *BRCA2* mutation was estimated as 7%. *BRCA1* and *BRCA2* mutation status was also investigated in an Australian cohort of 60 familial MBC cases [15]. Among these there were 28 carriers (3 *BRCA1* and 25 *BRCA2*) and 32 non-carriers with strong family histories. In comparison with FBC there was larger proportion of BRCA2 tumours, (43% versus 8%), and underrepresentation of *BRCA1* tumours (5% versus 14%), suggesting significant differences in the genetic aetiology of MBC and FBC. In a study of 261 Israeli MBC cases there were 21 *BRCA2* with 6174delT and 8 *BRCA1* with 185delAG mutations were found [16]. There was a similar proportion of *BRCA1* and *BRCA2* mutation carriers were found among Ashkenazi and non-Ashkenazi Jews (12.8% and 9.1%).

Other Susceptibility Genes

BRCA1/2 mutations account for less than 25% of familial FBC cases so alternative susceptibility genes have been sought, with varying degrees of success, These include *PALB2*, androgen receptor gene, *CYP17*, *CHEK2 and RAD51B*.

PALB2

This is the acronym for "partner and localiser of *BRCA2*" and the *PALB2* encodes a protein which maintains the nuclear placement and stability of *BRCA2*, enabling DNA repair of double strand breaks. Mono-allelic mutations of *BRCA2* and *PALB2* increase risk of FBC and bi-allic mutations are associated with Fanconi anaemia, Rahman et al. sequenced *PALB2* in DNA from 923 individuals with familial breast cancer and found truncating mutations in 10 (1.1%) as compared with none of the 1084 controls [17]. One of these mutations was found in a member of a family with

both MBC and FBC cases suggesting that *PALB2* mutations might increase the risk of MBC.

Adank et al. investigated *PALB2* mutations among 12 MBC and in one case found a truncating *PALB2* mutation, c.509_510delGA [18]. Ding et al. screened 115 MBC cases and found *BRCA2* mutations in 18 (16%) [19]. Of the 97 without *BRCA2* mutations one male had a *PALB2* mutation. Because of this the authors recommended screening all MBC for *PALB2* mutation regardless of family history. Blanco et al. determined the incidence of PALB2 mutations in 131 Spanish *BRCA1*/*BRCA2*-negative breast/ovarian cancer families in which there was ≥1 MBC [20]. In one family there was a *PALB2* deletion suggesting that *PALB2* germline mutations are not more frequent in families with MBC cases.

Fernandes et al. sequenced DNA from 1478 breast cancer patients who had no *BRCA1/2* mutations and divided them into high risk (955) or lower risk (523) [21]. High risk cases had breast cancer before age 50 or a relative developing the disease before age 50, or one MBC or ≥2 relatives with breast cancer aged <50 years. Overall 12 *PALB2* mutations were found. In the high risk individuals there were 10, including one MBC, compared with 2 in the low risk group, with no significant difference in prevalence. From a group of 8 MBC patients Vietri et al. identified a truncating mutation of *PALB2* designated c.1285_1286delAinsTC [22]. This does suggest that *PALB2* should enter the pantheon of MBC susceptibility genes.

Recently, Silvestri et al. used whole-exome sequencing (WES) and targeted gene sequencing to examine the significance of *PALB2* in 48 sporadic MBC cases from an Italian multicentre study [23]. They had found a truncating mutation (*PALB2*) c.419delA carried by the proband, her father, and paternal uncle all of whom had breast cancer and the nonsense mutation N-acetyltransferase 1 (NAT1) c.97C>T in her maternal aunt. Within the series of 48 MBC the c.1984A>T nonsense mutation was present in one case. They went on to conduct a case-control series of 433 *BRCA1/2* mutation-negative MBC and FBC cases with 849 male and female controls. NAT1 c.97C>T was not found in any of the participants, suggesting a small but important role for *PALB2* in MBC evolution.

RAD51C

The gene *RAD51C* is essential for homologous recombination repair and biallelic mutations are associated with Fanconi-like anaemia [24], and breast cancer in families not carrying *BRCA1* or *BRCA2* mutations [25]. *RAD51C* mutations were highly penetrant and present in 1.3% of families with ovarian and breast cancers. Orr et al. performed a genome wide association study of 823 European MBC cases with 2,795 controls [26]. A subsequent validation study was performed using independent sample with 438 cases and 474 controls. There were 17 SNPs that were significantly associated with MBC but in the validation set 2 emerged as significant, rs1314913 sited on intron 7 of *RAD51B* gene and rs3803662 which mapped to *TOX3* (16q12.1).

EMSY

Hughes-Davies et al. identified a protein EMSY, which binds *BRCA2* within exon 3, and is deleted in cancer [27]. The first line of the protein sequence reads SISTER so the first author named it after his sibling, Emsy, a Breast Care Nurse. The protein associates with chromatin regulators, and localises to repair foci following DNA damage. The *EMSY* gene is amplified in 13% sporadic FBC and is associated with worse survival. Navazio et al. sought to determine the role of *EMSY* amplification in specimens from 75 MBC cases using quantitative real-time PCR [28]. All had been analysed for presence of BRCA1/2 mutations. There was EMSY amplification in 35% of MBCs with a significant association between EMSY copy numbers and *BRCA1/2* mutations ($p = 0.03$). When specimens were subdivided into low and high amplification levels there was low amplification in *BRCA2*-associated cancers.

BCoRL1

BCL6 corepressor-like 1 (*BCoRL1*) gene is located on the X chromosome and encodes the protein BCoR-L1 involved in both DNA damage repair and transcription regulation. To investigate the role of *BCoRL1*, Lose et al. carried out a mutation analysis in 38 Australian families with a breast cancer disposition who did not have *BRCA1/2* mutations [29]. Within these families there were 11 MBC and within the coding region little variation was found. There was however a great deal of variation in *BCoRL1* in both cases and controls. This suggested that *BCoRL1* had very little influence on MBC susceptibility.

PIK3CA

Phosphatidylinositol 3-kinase, catalytic, alpha polypeptide (*PIK3CA*) encodes the p110 alpha (p110α) protein, a subunit of phosphatidylinositol 3-kinase (PI3K). PI3K signalling is involved in cell growth and division. Deb et al. used high resolution melting analysis and confirmatory signalling to look for somatic mutations in PIK3CA in 57 MBC cases [30]. Mutations were identified in 6 (10.5%) and were more frequent in non *BRCA2* patients (17% versus 0%).

Ataxia-Telangectasia Mutated (ATM)

In another study Deb et al. carried out high-throughput somatic sequencing on archival DNA from 48 familial MBCs [31]. Three had *BRCA1* mutations, 17 *BRCA2* mutations, and 28 were *BRCAX* (no known mutation). Seeking somatic mutations

and copy number changes in 48 genes implicated in cancer susceptibility they found 12 missense mutations included nine *PIK3CA* mutations (seven in *BRCAX* patients), two *TP53* mutations (both in *BRCA2* patients) and one *PTEN* mutation. Copy number losses of *ATM* were found in 34%.

Androgen Receptor Gene

In 1992 Wooster et al. reported 2 brothers with MBC, diagnosed at ages 75 and 55 who had androgen deficiency with hypospadias, inguinal canal testes and sparse trunk and limb hair (Reifenstein syndrome) [32]. Leucocyte DNA from both brothers was sequenced and this showed a guanine to adenine substitution in the androgen receptor gene in the DNA-binding domain. This mutation was not present in 100 AR alleles of unrelated individuals nor was it present in their sister. Following this, Lobacarro et al. sequenced leucocyte DNA from 13 French MBC cases and found that one with partial androgen insensitivity syndrome (PAIS) had a guanine-adenine point mutation at nucleotide 2185 [33].

A Swedish study sequenced the complete coding regions of both *BRCA2* and the *AR* gene in 34 MBC cases [34]. Although truncating mutations of *BRCA2* were found in 7 men, no AR gene mutations were identified although there was a reduced number of AR polyglutamine repeats among the *BRCA2* carriers. Within the *AR* gene at exon 1 there are variations in CAG repeats so Young et al. examined the lengths of the VCAG repeats in 59 MBC and 78 controls [35]. They found no difference in the distribution of alleles in the cases and controls.

Using a cohort of 32 Finnish MBC patients Syrjäkoski screened the entire coding region of the *AR* gene for mutations [36]. They found no germ-line mutations and when compared with Scandinavian population controls CAG and GGC repeat lengths were similar. Their conclusion was that the *AR* gene did not significantly predispose to MBC risk.

CYP17

The rate-limiting step in androgen synthesis is P450c17α hydroxylase coded by the steroid metabolism gene *CYP17*. A single base change at the 5` promoter was shown to be associated with polycystic ovary syndrome in females and male pattern baldness in men as a result of increased gene expression leading to elevation of androgen synthesis [37]. In a study of 76 MBC cases from South East Scotland, Young et al. examined whether the C allele of *CYP17* was associated with increased risk of cancer compared with the general male population [38]. There was a >4-fold increase in frequency of the C allele among MBC cases. In a subsequent case control study of 69 of the cases and 76 controls looking at a tetranucleotide repeat (TTTA) in intron 5 of *CYP17* there was no significant difference between the frequency in cases and controls [39].

Gudmunsdottir et al. examined DNA from 39 Icelandic MBC and 309 male controls to determine the role of a T (A1 allele) to C (A2 allele) TC polymorphism in the *CYP17* promoter region [40]. Of the cases, 15 (38%) were *BRCA2* mutation carriers. There was a higher frequency of the CC genotype among 999del5 carriers compared with non-carriers (33% versus 17%) but this did not achieve statistical significance. Overall, there appeared to be no association between *CYP17* and risk of MBC but this has to be interpreted with caution because of the relatively small numbers involved.

CHEK-2

CHEK2 (CHK2) encodes a G2/M checkpoint kinase which is involved with *BRCA1* associated DNA repair. The CHEK-2 Breast Cancer Consortium reported that the *CHEK2**1100delC mutation which inhibits kinase activity was present in 1.1% of the normal population [41]. In contrast, in MBC families without *BRCA1/2* mutations *CHEK2**1100delC was carried by 13.5%, leading to a tenfold increase in risk of MBC. This promising insight into a novel abnormality was unfortunately destined to be another false lead.

Genotyping of 300 breast cancer cases and 1665 controls from New York revealed *CHEK2**1100delC was present in only 3/300 cases including those with a family history or a personal history of breast cancer of whom 16 were MBC cases [42]. The mutation was found in 5/1665 controls and the authors concluded that testing for *CHEK2**1100delC was of limited applicability in North Americans with a family history of breast cancer.

Neuhausen et al. genotyped 109 MBC from the USA and 79 from the UK, with 138 age-matched controls from the US and 3749 from the UK [43]. The *CHEK2**1100delC mutation was not present in any of the US cases but found in 1 control. Similarly none of the UK MBC cases carried the mutation which was present in 20 UK controls. This implied that the relative risk of MBC in carriers was substantially smaller than previously predicted and did not explain familial aggregation of MBC. Ohayon et al. reported results from Israel in 54 MBC and 146 population controls which showed that none of the MBC cases carried the *CHEK2**1100delC mutation [44]. Similarly low or negative *CHEK2**1100delC carrier rates have been reported in other studies from the UK, US, and Finland.

In a search for other susceptibility genes a two-stage genome-wide association study was conducted which included 4,398 FBC cases and 4,316 controls [45]. A shortlist of 30 single nucleotide polymorphisms (SNPs) were tested for confirmation in 21,860 cases and 22,578 controls SNPs in five novel independent loci were consistently associated with FBC and 4 contained plausible causative genes (*FGFR2*, *TNRC9*, *MAP3K1* and *LSP1*).

To determine if these variants contributed to MBC risk, Orr et al. genotyped 433 male breast cancer cases and 1,569 controls [46]. In a case-control study they evaluated the 12 SNPs that had the strongest associations with FBC. Results are summarised

Table 4.2 Ratio of odds ratio for MBC: odds ratio for FBC for 12 risk loci for FBC [46]

SNP	Chromosome	OR MBC/OR FBC	X^2	P value
rs11249433	1p110.95	0.95	0.43	0.50
rs13387042	**2q35**	**1.19**	**4.53**	**0.03**
rs4973768	3p24.1	1.07	0.68	0.41
rs10941679	5p12	1.03	0.09	0.77
rs16886165	5q11.2	0.81	3.12	0.08
rs9383938	6q25.1	1.22	2.4	0.12
rs13281615	8q24.21	1.02	0.036	0.85
rs865686	9q31.2	0.95	0.29	0.59
rs2981579	10q26.13	0.96	0.32	0.57
rs3817198	11p15.5	0.87	2.6	0.10
rs3803662	**16q12.1**	**1.19**	**4.1**	**0.04**
rs6504950	**17q22**	**0.84**	**4.09**	**0.04**
All SNPs			**22.769**	**0.03**

in Table 4.2. There were 2 SNPs for which the OR for MBC was significantly higher than that for FBC, rs13387042 and rs3803882 (2q35). 2q35 had the strongest association with risk of MBC (OR = 1.48) which was more than twice the OR for FBC. It is very interesting that in *FGFR2*, the main SNP associated with ER-positive female breast cancer, does not appear to be associated with MBC suggesting that ER status is unrelated to the overlap in SNP associations between MBC and FBC When the estimates derived each of the SNPs are combined there is a significant difference between MBC and FBC. It should be possible to identify those *BRCA2* carriers who are at higher risk using common predisposition SNPs.

Johansson analysed 66 MBC tumours using high-resolution tiling bacterial artificial chromosome (BAC) arrays and compared the results with a genomic data set of 359 FBC tumours [47]. In MBC there were more genomic gains often involving whole chromosome arms but genomic losses were less frequent. High-level amplifications were also less frequent in MBC. Among MBC two subgroups emerged; male-complex and male-simple. The former was similar to the luminal-complex FBC subgroup. In contrast, the male-simple subgroup was found only in men.

Recently Piscuoglio et al. reported results of targeted capture massively parallel sequencing to determine somatic mutations in 64 MBCs, all of which were ER+ve and HER2-ve [48]. Mutations were found most frequently in *PIK3CA*, *GATA3*, *FLG* and *PLEC* but the only significantly mutated gene was *PIK3CA*. Genes frequently mutated in FBC such as *MAP2K4* and *NCOR1* were not mutated in MBC.

Genetic Testing

Once *BRCA1/2* had been identified genetic testing became a reality but was likely to be associated with adverse psychological effects. Based on a hereditary cancer registry, 327 individuals from 33 families were asked to participate in a study

examining depression before and after counselling and genetic testing [49]. Of the families 27 were linked to *BRCA1* mutations and 6 to *BRCA2*. All had previously given blood samples which had been examined for mutations but results were not known to the participants who were contacted by letter and asked if they wished to know if they carried the mutation. Of those agreeing, 396 completed a baseline telephone questionnaire which included the Intrusion Subscale of the Revised Impact of Event scale to assess cancer-related stress and the Center for Epidemiologic Studies Depression Scale (CES-D). Of these 227 (57%) wanted to know their carrier status. After an education session conducted by an oncologist according to a semi-structured protocol, those agreeing were then given their results and a follow-up questionnaire was sought one month later. This was completed by 86% of females but only 76% of males.

Participants were divided into three groups, carriers (97), non-carriers (109) and decliners (121). Baseline depression scores were no different in the three groups but one month later depression affected 19% of decliners compared with 8% of non-carriers and 14% of carriers. Among those with high stress levels at baseline (113), individuals who declined were more likely to be depressed one month later, rising from 26% to 47% whereas there was a fall for non-carriers from 41% to 11% and little change in carriers (20% to 23%).

Using a cohort of 102 Italian MBC patients the usefulness of four different predictive models for likelihood of BRCA1/2 mutations was examined [50]. In this study, the BRCAPRO version 5.0 performed best with the highest combination of sensitivity, specificity, NPV and PPV for the combined probability and for the discrimination of BRCA2 mutations. In individuals with no family history of breast or ovarian cancer, BRCAPRO 5.0 reached a high discriminatory capacity (AUC = 0.92) in predicting BRCA2 mutations with values of sensitivity, specificity, NPV and PPV of 0.5, 0.98, 0.97 and 0.67, respectively. This latter group may present challenges for counselling in genetic clinics.

The German Consortium for Hereditary Breast and Ovarian Cancer amassed data on 21,401 families who had undergone counselling after full pedigree ascertainment with cancer status of all family members [51]. The *BRCA1/2* mutation status was available for each index patient. *BRCA1/2* mutations were present in 24.0% with the highest frequencies in families with one breast and one ovarian cancer (42%), or ≥2 ovarian cancer cases (42%). If there was one MBC and ≥1 FBC or OC, mutations were present in 36%.These data are useful for healthcare professionals to decide who should undergo genetic testing for hereditary breast and ovarian cancer.

Histopathology

In a cohort of 60 familial MBCs, including 3 *BRCA1* and 25 *BRCA2* mutation carries, and 32 *BRCAX* the histology was investigated [52]. There were no differences in histology related to mutation status or when comparing familial with non-familial

MBC. This was in contrast to the differences seen in familial and non-familial FBC. Unlike familial FBC, the spectrum of histology in familial MBC was closer to sporadic MBC with 77% being invasive ductal carcinoma of no special type (IDC-NST), 3% invasive lobular and 7% invasive papillary carcinoma. Most cancers were luminal (90%), with infrequent HER2 (9%) and rare basal (2%).

The Consortium of Investigators of Modifiers of BRCA1/2 studied the histological features of 419 MBC tumours from *BRCA1/2* carriers and compared this with the pathology from 9675 FBC *BRCA1/2* carriers and with results from 6351 MBC in the Surveillance, Epidemiology, and End Results (SEER) database [53]. There was a decrease in grade with increasing age among *BRCA2* carriers. *BRCA2* cancers in males were of higher stage than *BRCA2* FBC and more frequently oestrogen receptor-positive. Apart from grade, similar associations were seen when comparing *BRCA1* MBCs and FBCs. Furthermore, *BRCA2* MBCs were of higher grade than tumours from the SEER database. This suggests that *BRCA2*-associated MBC is more likely to be aggressive, that is of high histological grade). These findings could lead to the development of gender-specific risk prediction models and guide clinical strategies appropriate for MBC management.

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Chapter 5
Histopathology

Abstract There is at present a mismatch between the extensive histopathological information available on MBC and a lack of long-term follow up information to transform this into accurate prognostic data. Invasive ductal carcinoma predominates with variants of papillary and secretory carcinoma occurring more proportionally more frequently in MBC than FBC. Pure mucinous carcinomas are associated with a good prognosis whereas micropapillary invasive cancers may be more aggressive. Invasive lobular carcinomas are rare and sometimes occur in males taking estrogens and individuals with Klinefelter's syndrome. Management of breast sarcoma is surgical whenever this is possible but the role for chemotherapy and radiotherapy has yet to be determined.

If pathology is nothing but physiology with obstacles, and diseased life nothing but healthy life interfered with by all manner of external and internal influences then pathology too must be referred back to the cell. Rudolf Virchow

Introduction

No single institution sees enough cases of MBC to achieve a series of meaningful size for histological evaluation and comparison with FBC. Those large published series that are available for analysis have been derived from national studies [1–3]. In 1948, Norris and Taylor from the US Armed Forces Institute of Pathology (AFIP), reviewed the specimens from 113 cases of MBC which comprised 2.4% of the total pool of breast cancer material.

They reported that the gross features of MBC were similar to FBC, with most being firm gritty and containing yellowish and haemorrhagically streaked foci. Because of the absence of surrounding breast tissue most were more evident than FBC. Microscopically, 8 (7%) were ductal carcinoma in situ (DCIS). The predominant histological type was ductal carcinoma of no special type, diagnosed in 92 (81%).

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Table 5.1 Comparative histology and IHC of MBC and FBC [7]

Feature	MBC	FBC
Grade III	85%	50%
ER+ve	81%	69%
PR+ve	63%	56%
HER2+ve	5%	24%
P53	9%	28%
Bcl2	79%	76%

Results are summarised in Table 5.1, which shows that 9 (10%) were of papillary type. Although Paget's cells were seen in the epidermis of 12 (11%), no clinical cases of Paget's disease had been diagnosed.

Visfeldt amassed 265 Danish cases of MBC and was able to histologically type and grade 187 of them. The predominant type was invasive ductal carcinoma and in this series, no cases of invasive lobular cancer were seen. It was possible to grade 150 of the invasive ductal carcinoma of which 44 (29%) were grade I, 81 (54%) grade II and 25 (17%) grade III. Special types included medullary 4, papillary 5, cribriform 5, and Paget's disease 3.

Using data from the Swedish Cancer Registry acquired between 1958 and 1967 Hultborn et al. reported 190 cases of male breast cancer and the specimens underwent central histopathological review [4]. All of the cancers were of ductal type but four were DCIS. There were no pure mucinous cancers but three showed partial mucinous change and another three showed medullary change. The Sloane-Kettering Memorial group amassed 104 MBC patients with 106 breast cancers [5]. Most were IDC but there were two medullary/tubular cancers. Donegan et al. reviewed 217 cases of MBC reported to 18 tumor registries in Wisconsin and reported that they were overwhelmingly of invasive ductal type 196/217 (90%) [6]. There were 12 DCIS, 4 invasive papillary carcinomas, 1 phyllodes tumour, 1 leiomyosarcoma and 1 inflammatory carcinoma.

Muir et al. conducted a case control study with 59 cases from the Saskatchewan Cancer Foundation collected between 1970 and 1996 [7]. The controls were stage matched FBC cases and histological review of tumour grade was carried out together with IHC for ER, PR, HER2, p53 and Bcl2. Results are outlined in Table 5.1. Of the MBC specimens, 85% were grade III, compared with 50% of FBC but MBC were more frequently ER+ve (81% vs 69%). Most noticeably HER2 amplification was less frequent in MBC (5% versus 17%) as was overexpression of p53 (9% versus 28%).

Between 1979 and 1999, Ben Dhiab et al. collected 123 Tunisian MBC cases, summarised in [8] In 2006 a larger series of 759 archival cases from the AFIP was reported by Burga et al. The majority, 85% were invasive ductal carcinoma (IDC) and 26 were a mixture of IDC and mucinous with 21 being pure mucinous cancers. Carcinoma associated with Paget's disease of the nipple was reported in 34 cases (4%). There were 19 cases where the malignancy was a secondary within the breast with the commonest primary site being melanoma. Pure invasive lobular carcinoma was diagnosed in only three cases with a mixed ductal/lobular pattern in another 3.

Table 5.2 Histopathology in large series of MBC

Author	N	IDC	Papillary	Mucinous	Paget's	DCIS	Other
Norris 1969 [1]	113	92	9	1	0	8	3
Visfeldt 1973 [2]	265	157	5	0	3	0	22
Hultborn 1987 [4]	190	166	12		5	4	
Borgen 1992 [5]	106	87				16	3
Donegan 1998 [6]	217	196		1		12	4
Ben Dhiab 2005 [8]	123	113				3	5
Burga 2006 [3]	759	645		21	34		
Cutuli 2010 [9]	489	462					
Bourhafour 2012 [10]	127	122			2		3
Aggarwal 2012 [11]	51	45				5	1

A large French cohort of 489 cases was reported by Cutuli et al. in 2010 [9]. There were 462 (95%) which were IDC and of these 22% were grade I, 51% grade II and 20% grade III. Bourhafour et al. from the National Institute of Oncology, Rabat Morocco acquired data on 127 MBC seen between 1985 and 2007 [10]. IDC comprised 96% of the cases and 82% of these were grade II/III. There were 2 with Paget's disease and 2 ILC. Aggarwal et al. reported 51 cases of MBC from the Veterans Affairs Medical Center and of these 90% had IDC with 5 DCIS and one sarcoma [11]. A series of 42 Nigerian MBC cases reported that 15 were grade I, 7 grade II and 20 grade III [12]. There were 37 (88%) IDC, 1 papillary, 2 ILC and 2 mixed IDC/ILC (Table 5.2).

Intracystic Papillary Carcinoma

Like Gaul, intracystic papillary lesions may be divided into three parts: benign, non-invasive (DCIS) and invasive. All these have been described in males as rare lesions but for the most part long-term follow-up has been lacking so the behaviour of these diverse intracystic abnormalities is only patchily understood.

Benign Papilloma

In 1946 Moronet reported a 31 year old man with a 2 year history of intermittent bloody right nipple discharge who was treated by total mastectomy [13]. Histology showed extensive intraductal papilloma (IDP) with no evidence of malignancy. Reviewing paediatric breast lesions seen at the Toronto Hospital for Sick Children over a 40 year period, Simpson and Barson described a 7-month-old Native American boy with a lump under the right nipple of the right breast, present for 4 months [14]. The lump measured 5 cm and was excised together with the nipple and proved to be a benign papilloma. This was the youngest male case of benign IDP

Table 5.3 Male benign papilloma cases

Author	Patient age	Presentation	Treatment
Moroney 1946 [13]	31	Bloody discharge	Mastectomy
Simpson 1969 [14]	7 months	Lump	WE
Volmer 1984 [15]	26	Lump	WE
Detraux 1985 [16]	51 52	Serous discharge Bloody discharge	WE WE
Sara 1987 [17]	71	Lump	WE
Martorano Navas 1993 [18]	82	Lump	Mastectomy
Georgountzos 2005 [19]	56	Lump & discharge	WE
Shim 2008 [20]	44	Lump & discharge	WE
Yamamoto 2006 [21]	57	Lump & discharge	WE
Durkin 2010 [22]	14	Lump	WE
De Vries 2016 [23]	29	Lump	WE

and subsequent reports have been summarised in Table 5.3. Volmer et al. reported a 26 year-old male who had a pituitary adenoma and gynaecomastia and presented with mass that was an IDP [15].

Detraux et al. investigated a series of 7 males with nipple discharge using galactography [16]. Of these, two men had IDPs, two had intraductal carcinoma and there was one abscess and two cases of duct ectasia. Sara et al. described a 71 year-old man who had been taking phenothiazines for more than 10 years and complained of a coffee-coloured left nipple discharge [17]. There was a 10 cm mass which on resection proved to be an IDP. An 82 year old with a 10 cm mass was reported by Martorano Navas et al. and because of cytological atypia a mastectomy was performed for this IDP [18]. Georgountzos et al. reported a 56 year-old man who gave a 2 year history of intermittent bloody discharge from the left nipple [19]. He was taking no medications and aspiration yielded atypical cells so excision was performed which confirmed IDP.

Shim et al. reported a 22 year-old with a mass fixed to the chest wall which was a complex cystic lesion on ultrasound and proved to be an IDP after excision [20]. A second case of IDP after long-term phenothiazine to a 57 year-old schizophrenic was described by Yamamoto et al. [21]. Durkin et al. reported a 14 year-old boy with an IDP which had caused unilateral breast enlargement [22]. The case presented by De Vries et al. was a 29 year-old male with a 1 cm lump beneath the left nipple which was lobular and solid on ultrasound [23]. These cases indicate that IDP can occur at any age in the male and usually presents as a lump, sometimes with an associated blood stained discharge. The treatment has been surgical to date but it is possible that smaller lesions could be extirpated via a ductoscope.

Intracystic Papillary Carcinoma (DCIS)

These rare lesions may be indistinguishable clinically, radiologically and cytologically from IDP. Histologically the papillary lesion contains round/polyhedral carcinoma cells with mild atypia, rare mitoses and no stromal invasion. As Table 5.4

Table 5.4 Male cases of intracystic papillary carcinoma

Author	Patient age	Presentation	Treatment	Outcome
Noguchi 1983 [24]	80	Lump	TM	Alive 3 years
Watanabe 1986 [25]	46	Lump	MRM	?
Sasahashi 1992 [26]	64	Lump	RM	Alive 11 months
Sonksen 1996 [27]	62	Lump	TM & AS	Alive 1 year
Kato 1997 [28]	54	Lump	MRM	Alive 7 years
Imoto 1998 [29]	62	Lump	WE	Alive 1 year
Anan 2000 [30]	75	Lump	MRM	Alive 6½ years
Tochika 2001 [31]	66	Lump	MRM	?
Pacelli 2002 [32]	67	Lump	TM &SNB	?
Inoue 2003 [33]	73	Discharge	WE	Alive 4 years
Andres 2003 [34]	74	Lump	WE	?
Kihara 2004 [35]	68	Lump	MRM	?
Kinoshita 2005 [36]	71	Lump & D	SM	>
Sinha 2006 [37]	75	Lump	WE	Alive 1 year
Yamamoto 2006 [21]	57	Lump & D	WE	Alive 1 year
Dragoumis 2008 [38]	75	Lump	WE & ANC	Alive 4 years
Romics 2009 [39]	44	Lump	TM & SSM RT	?
Pandey 2010 [40]	50	Lump	WE	Alive 1¼ years
Kelessis 2011 [41]	61	Lump	MRM	?
Muallaoglu 2012 [42]	48	Lump	WE	Alive 2 years
Hariprasad 2013 [43]	50	Lump	TM & SNB	Alive 2 years
Al Saloom 2015 [44]	53	Lump	MRM	Alive 2 years
Hu 2016 [45]	59	Bloody discharge	TM	?

shows the cases occur predominantly in the sixth and seventh decades, usually presenting as a painless breast lump [21, 24–45].

Imoto and Hasebe reported a 62 year-old with intracystic papillary carcinoma together with four cases from the Japanese literature [29]. The first reported preoperative diagnosis by ultrasound-guided core biopsy came from Pacelli et al. [32] The predominant surgical intervention has been either modified radical (MRM) or total mastectomy (TM). There are no 5-year follow-up data but the early outcomes indicate a good prognosis for males with intracystic papillary carcinoma in the absence of adjuvant radiotherapy or systemic therapy.

Invasive Papillary Carcinoma

Invasive papillary carcinoma is a rare but sometimes aggressive variant of MBC. It is characterised by delicate pseudopapillary fronds without a fibrovascular core together with tubuloalveolar structures floating freely within clear lacunae. In 1958 Benet described a 64 year-old schoolmaster who gave a 2 year history of a gradually

Table 5.5 Male invasive papillary carcinoma

Author	Patient age	Presentation	Treatment	Outcome
Benett 1958 [46]	64	Lump	TM	Alive 4 years
Blaumeiser 2002 [47]	77	Lump	MRM	?
Zeppa 2003 [48]	55	Lump	WE	?
Erhan 2005 [56]	66	Lump	WE	Stage IV
Khalbuss 2006 [49]	67	Lump	WE	
Pant 2009 [50]	78	Lump	MRM	?
Arora 2010 [51]	62 81	Lump Lump	TM TM	Alive 1 year Alive 1 year
Yoshida 2010 [52]	64	Lump	WE & ANC	?
Tsushimi 2013 [54]	63	Lump	MRM	Alive 1 year
Vagholkar 2014 [55]	55	Lump	MRM	Alive 6 months
Trepant 2014 [57]	73	Lump	TM & SNB	?

enlarging right breast lump treated in Mauritius by mastectomy [46]. This was reported as an intraductal papilloma with probable malignant change. He remained well without recurrence 4 years later (Table 5.5). Blaumeiser et al. reported a 77 year-old male with a breast lump [47]. As part of the work-up they carried out breast MRI. Because of the patient's dyspnoea MRI was modified using T1 weighted spin echo (SE) sequence which outlined an irregular tumour mass hypodense on T2 weighted sequence. TI SE after gadolinium showed inhomogeneous enhancement of signal. These findings did not lead to a definite pre-operative diagnosis. He was treated by modified radical mastectomy with 0/9 nodes involved.

Zeppa et al. studied the cytology from a 3 cm breast lump in a 55 year-old male [48]. Smears were hypercellular with isolated cells and papillary structures. Cells showed tall and well-defined cytoplasm. DNA histogram showed aneuploidy and histology confirmed papillary carcinoma with lymphatic invasion extending to the chest wall. Erhan et al. reported a 66 year-old man with a 1.5 cm grade III invasive micropapillary carcinoma, who had lung and adrenal metastases at the time of diagnosis. These micropapillary invasive cancers are often aggressive and associated with early lymphovascular invasion. Khalbuss et al. described a 67 year-old with known prostate cancer who complained of a retroareolar painless mass [49]. Fine needle aspiration cytology yielded a cellular specimen with papillary clusters. IHC of the cell block was positive for mammaglobin and negative for PSA. Wide excision confirmed a grade II infiltrating papillary carcinoma with associated DCIS. Pant et al. made a pre-operative cytological diagnosis of papillary carcinoma which proved histologically to be a moderately differentiated invasive papillary carcinoma [50]. Arora et al. reported two cases of invasive papillary carcinoma, both treated by mastectomy and recurrence-free after a year [51].

Loss of heterozygosity (LOH) on 16q has been reported in infiltrating papillary FBC but Yoshida et al. reported no LOH in their 64 year old male patient [52]. Petinato et al. reported a series of 62 cases of micropapillary invasive

cancer of whom one was male [53]. Of the 41 patients with follow-up data, 71% developed local relapse after an average of 30 months and 49% had died of metastatic disease indicating the poor prognosis of this particular cancer. After a core biopsy had shown invasive cancer Tsushimi et al. performed a mastectomy and axillary clearance for a node negative invasive papillary carcinoma [54]. Vagholkar also carried out a modified radical mastectomy for a 55 year-old male with invasive papillary carcinoma who, like the others in this series, proved to be node negative [55].

Invasive Lobular Carcinoma

Because of the absence of lobular differentiation in normal males, invasive lobular carcinoma is a rare form of MBC comprising <2% of cases. It is characterised microscopically as sheets of small rounded cells often displaying "Indian filing", that is, single file cellular infiltration. Usually there is pure ILC but sometimes alveolar type is seen and less frequently pleomorphic, signet cell histiocytic or apocrine changes are seen. With immunohistochemical (IHC) staining the cells are e- cadherin negative.

Originally called small cell carcinoma this was originally described by Norris & Taylor in 1969 [1]. Since then there has been a steady dribble of cases and these are summarised in Table 5.2. Two cases of ILC out of a series of 16 MBC cases seen at the Medical College of Virginia were described by Giffler and Kay in 1976 [58]. In 1986 Sanchez et al. reported a case of invasive lobular carcinoma (ILC) of the breast in a 61 year old white phenotypic male [59]. After the diagnosis had been made the patient underwent endocrine and karyotypic analyses. Serum testosterone was within the normal range but there was elevation of FSH and LH with reduced urinary 17-ketosteroids. The patient's leukocytes were subjected to cytogenetic analysis with 94% of the cells being 47XXY (Klinefelter's).

Within a series of 4 cases of MBC, Chandrasekaran et al. reported that two were of Klinefelter's genotype and both of them had ILC [60]. Briest et al. treated a 52-year-old man with ILC who was subsequently shown to be carrying a pathological mutation of *BRCA2* [61]. Mariolis-Sapsakos et al. reported a case of ILC in a 74 year old man with two children and a duplication of the heterochromatic region of chromosome 1 [62]. They reviewed the available literature and found that there were 18 previous cases, of whom 9 (50%) had cytogenetic analyses performed. Klinefelter's, 47XXY was confirmed in 3 (33%).

Moten et al. used the Surveillance, Epidemiology, and End Results database 1988-2008 to identify patients with ILC [63]. Of the 133,339 cases 171 (0.1%) were male who were more likely than women to have grade III cancers (26% versus 15%. Additionally, men were more likely to present with stage IV disease (9% versus 4%. Spencer and Shutter described the first case of a 58 year-old man who presented with bilateral ILC and increase in girth as result of carcinomatosis [64].

Pleomorphic Invasive Lobular Carcinoma

Maly et al. reported a 44 year-old Ashkenazi father of 3 who presented with a left breast lump which on biopsy proved to be a pleomorphic invasive lobular carcinoma (PILC) [65]. On microscopy these aggressive cancers contain hyperchromatic, pleomorphic cells with high nuclear/cytoplasmic ratio. Nucleoli are prominent and the cytoplasm is moderately eosinophilic with cells arrayed in dyscohesive sheets which lack e-cadherin expression. Cells often display signet-ring formation together with intracytoplasmic neo-lumina with targetoid appearance.

Table 5.6 Features of MBC cases with ILC

Author	Patient age	Feature	Ethnicity	Karyotype
Norris 1969 [1]				
Giffler 1976 [58]	67 74		US Black US Black	
Yogore 1977 [67]	56	Nil	US Black	
Schwartz 1982 [68]	66			
Vercoutere 1984 [68]				
Wolff 1983 [70]	55 75		US white US Black	
Sanchez 1986 [59]	61		Spanish	47XXY
Aghaudino 1987 [71]	75 60		Nigerian Nigerian	
Nance 1989 [72]	82	Nil	US white	
Sawabe 1992 [73]	74		Japanese	
Michaels 1994 [74]		Nil	US white	46XY
Joshi 1996 [75]	31			
San Miguel 1997 [76]		Cimetidine	Spanish	46XY
Iwase 1997 [77]			Japanese	
Scheidbach 2000 [78]	85	German		46XY *BRCA1*
Chandrasekaran 2001 [60]	53 73		English	47XXY 47XXY
Koc 2001 [79]	52		Turkish	46XY
Sano 2001 [80]				
Maly 2005 [65]	44	PILC		XY
Erhan 2006 [56]	64	Nil		
Madri 2006 [81]	56			46XY
Spencer 2009 [64]	58	Carcinomatosis	US white	
Mariolis-Sapsaks 2010 [62]	74	Nil	Greek	46XY
Rohini 2010 [66]	55	PILC	Indian	
Ninkovic 2012 [82]	56	RT & Chemo	Serbian	
Ishida 2013 [83]	76	PILC	Japanese	
Melo-Abreu [86]	52	Nil	Portuguese	

Since that first description of PILC in MBC there have been further sightings. Rohini et al. described a 55-year-old male with a left breast lump present for 5 months [66]. There were no known risk factors such as oestrogen or drug use. Despite having a reputation for being an aggressive lesion all three cases were alive without recurrence at the time of reporting. Cases are summarised in Table 5.6 [1, 56, 58, 60, 65, 67–84].

Secretory Cancer

Secretory carcinoma is characterised by two particular histological features: presence of extensive intracellular and extracellular secretions and within the cells, granular eosinophilic cytoplasm. This rare cancer was first described by McDivitt & Stewart as juvenile carcinoma because of the young age at presentation [85]. It was subsequently dubbed secretory breast cancer (SBC) by Tavassoli et al. who reported 19 cases of whom one was a 9 year-old boy [86]. They found two cell types, A and B. The former were slightly granular with extensive secretions within the malignant cells and also in the extracellular lumens. Type B cells were round/polygonal shaped with granular or vacuolated cytoplasm. Invariably there was a mixture of the two cell types. The tumour was treated by local excision and the patient remained disease-free 21 months after surgery.

It is likely that the first case reported was a 6-year old boy with a left breast lump [87]. The biopsy was sent to several notable pathologists including Dr. Stewart and all were agreed that this was an adenocarcinoma although Dr. Stewart commented that he had never seen a cancer in so young an individual. Reviewing 9 breast tumours in infants and children seen at the Hospital for Sick Children, Toronto, over a 40-year period Simpson & Barson reported a 5 year-old boy with a secretory carcinoma. This was treated by excision and there had been no recurrence at the time of publication [88].

The full list of 25 reported cases of SBC is summarised in Table 5.7 [86–108]. Karl et al. reported a 3-year-old boy with a node positive SBC, treated by radical mastectomy, who survived without recurrence for an unspecified duration [91]. Unfortunately because of an urge to publish details of these rare cases very few studies reported a follow-up of ≥5 years. The exception was the report of Krausz et al. from the Hammersmith Hospital which included four females and one male [94]. Recurrence occurred in four cases after 3, 5, and 8 in females and 20 years in the MBC case. The latter patient presented in 1961 with a longstanding lump and was treated by total mastectomy and axillary irradiation. In 1981, after developing arm lymphoedema he was found to have axillary nodal, scalp and hepatic metastases which did not respond to chemotherapy.

In 2002, Tognon et al. reported that SBC expressed the ETV6-NTRK3 (EN) gene fusion previously identified in paediatric mesenchymal tumours [109]. The gene fusion product was a chimeric tyrosine kinase which was able to transform

Table 5.7 Male cases of secretory carcinoma

Author	Patient age	Receptors	EN	Outcome
Hartman 1955 [87]		–		
Simpson 1969 [88]	5	–		Alive 4 years
Tavassoli 1980 [86]	9	–		Alive 1.75 years
Karl 1985 [89]	3	–		–
Kuwabara 1988 [90]	66	ER−ve/PR−ve		Alive 0.75 year
Roth 1988 [91]	23	–		Alive 4 years
Krausz 1989 [92]	24	–		Died 20 years post rec
Serour 1992 [93]	17	ER−ve/PR+ve−		Alive 5 years
Lamovec 1994 [94]	20	ER+ve/PR+ve		Alive 1 year
Pohar-Marinsek 1994 [95]	20	ER−ve/PR+ve		Alive 0.5 year
Vesoulis 1998 [96]	33	ER+ve/PR+91ve		–
Kameyama 1998 [97]	50	ER+ve		–
Chevallier 1999 [98]	9	ER−ve/PR−ve		Alive 3.75 years
Yildirim 1999 [99]	11	ER−ve		Alive 1 year
Bhagwandeen 1999 [100]	9	ER−ve/PR−ve		
Titus 2000 [101]	9	ER−ve/PR−ve		Alive
De Bree 2001 [102]	17	ER−ve/PR−ve		Alive 0.75 year
Niveditha 2004 [103]	19	ER−ve/PR−ve		–
Grabellus 2005 [104]	46	ER−ve/PR-v103	Positive	–
Gabal 2011 [105]	10,319	ER−+ve/PR−ve		–
Li 2012 [106]	10 18	ER−+ve/PR−ve ER−+ve/PR−ve		Alive 1 year Alive 1.1 years
Sharma 2015 [107]	12	ER−ve/PR−ve		Alive 0.5 year
MIsra 2016 [108]	8	ER+ve/PR−ve	Positive	Alive 3 years

EN ETV6-NTRK3

fibroblasts. Using reverse transcriptase-PCR (RT-PCR) and fluorescence in situ hybridization (FISH) to look for EN fusion transcripts they examined 13 SBC and 5 ductal carcinomas. There was positivity for EN in 12/13 SBC, the one exception being the male. Following this Grabellus et al. described a 46-year-old male-to-female transsexual who had undergone sexual reassignment surgery including augmentation mammoplasty and been taking long-term estrogens [106]. At the age of 46 it dislocation of the silicone implant was suspected and at the time of surgery a tumour was found which proved to be an SBC with ETV6–NTRK3 gene fusion positivity. The most recent reported case of secretory cancer was diagnosed in an 8 year-old boy who was treated by mastectomy and negative sentinel node biopsy [110]. The 1.4 cm cancer expressed ETV6-NTRK3 (EN) gene fusion, confirming the diagnosis. He was alive without recurrence 3 years later.

Adenoid Cystic Carcinoma

Adenoid cystic carcinoma (ACC) is a very rare MBC with the most common primary site being a salivary gland. It is identified histologically as having a biphasic pattern, comprising laminate and pseudocystic spaces lined by myoepithelial cells, together with glands epithelial-lined glands. The first male case was a 37-year old reported by Woyke et al. [110]. He was treated by local excision and relapse locally after 5 and 7 years. Features and outcome are shown in Table 5.8 [110–118].

Verani et al. reported a 78-year-old male with a tender right breast lump present for approximately 10 years [111]. Frozen section made the diagnosis of ACC and he was treated by radical mastectomy. Although there was no axillary nodal involvement nevertheless he relapsed and died 9 months after surgery. Ferlito et al. reported a 60-year old, treated by simple mastectomy but without follow-up [114] and Hjorth et al. described a young man aged 20 with ACC [115]. Miliauskas et al. were the first to describe adenoid cystic carcinoma in a juvenile male breast [116]. Following subcutaneous mastectomy he was well without recurrence after 2½ years.

Kshirsagar et al. reported the case of an 82-year-old male with an ulcerating tumour in his left breast [117]. Modified radical mastectomy was performed and the lesion was an adenoid cystic carcinoma, Periodic acid Schiff (PAS) positive, with three involved axillary nodes. Postoperative radiotherapy was refused and 2 years later he returned with chest wall recurrences, treated by wide excision with a split thickness skin graft. There was no further relapse at 9 months. Liu et al. treated a 20 year old but with unknown outcome [117] and Yoo et al. reported 41-year old male who relapsed with pulmonary and bone metastases [119]. The 19-year-old reported by Tang et al. underwent radical mastectomy for a 30 mm ACC with 0/41 nodes involved. He was alive without recurrence 67 months later. With such heterogeneity of reporting and follow-up it is difficult to summarise the results of surgery for ACC. It appears that despite axillary nodal status being negative in all but one case nevertheless these cases are at risk of distant metastases possibly from lymphovascular invasion.

Table 5.8 Adenoid cystic cancer in males

Author	Patient age	Axilla	Outcome
Woyke 1970 [110]	37	−ve	Recurred
Verani 1973 [111]	78	−ve	Died
Ferlito 1974 [112]	60	−ve	?
Hjorth 1977 [113]	21	−ve	Alive 2 years
Milauskus 1991 [114]	13	−ve	Alive 2½ years
Kshirsagar 2006 [115]	82	+ve	Recurred 2 years
Liu 2012 [116]	20	−ve	?
Yoo 2013 [117]	41	−ve	Bone/lung mets
Tang 2015 [118]	19	−ve	Alive 5½ years

Mucinous Carcinoma

Mucinous carcinomas are either pure or mixed, the former having >90% mucinous component. Pure mucinous carcinomas may be associated with less aggressive behaviour. Reported frequency varies but in the largest series of 759 MBC cases subjected to histological review, 21 (3%) were mucinous [3]. Those cases which have been reported with accompanying clinico-pathological details are summarised in Table 5.9 [119–125]. Although the majority of cases were in their eighth or ninth decade, Fujikawa et al. reported a 35-year-old male with an enlarging right breast lump which had become painful [121]. Ultrasound showed a multiloculated cyst with mixed internal echoes resembling a phyllodes tumour. After mastectomy it was shown to be a mucin-producing cancer. The patient was recurrence-free 2½ years post-operatively.

Peschos et al. described the very unusual cases of an 86 your old male who presented with Paget's disease of the nipple and an underlying mucinous carcinoma which was ER/PR+ve [122]. Nodal involvement was more frequent than in FBC and Hammedi et al. reported a 75-year-old Tunisian man with pure mucinous carcinoma who had lymph node involvement but after mastectomy chemotherapy, radiotherapy, and endocrine therapy was disease-free 3 years later [123]. When ER status was determined, most of these lesions were ER+ve but Aggarwal et al. treated a male whose tumour was both ER and PR−ve [124]. Ingle et al. made a pre-operative diagnosis of mucinous carcinoma using fine needle aspiration cytology (FNAC). The tumour proved to be pure mucinous carcinoma but with axillary nodal involvement [125].

Dragoumis et al. described a 59-year-old male with a gradually increasing right retroareolar lump which was well demarcated with soft consistency [126]. After modified radical mastectomy it was confirmed as pure mucinous carcinoma with axillary nodal involvement. Ishida et al. reported a 63 year-old Japanese male with an ER+ve, PR−ve, HER2−ve cancer whom they treated by wide excision and negative sentinel node biopsy [127]. Follow-up data when available did not extend to 5 years but up to the time of reporting, none of the cases had died.

Mixed mucoid MBC, with >10% of the tumour comprising infiltrating ductal carcinoma IDC has been less commonly recorded. Sinha et al. described a 50 year old with a 20 mm grade II mixed mucoid MBC which was ER+ve [126]. He was treated by mastectomy and negative sentinel node biopsy, given tamoxifen and was

Table 5.9 Pure mucoid MBC

Author	Patient age	Nodal status	ER status	Survival
Fujikama 1998 [119]	35	?	?	A&W 30 months
Peschos 2008 [120]	86	?	+ve	?
Hammedi 2010 [121]	75	+ve	+ve	A&W 36 months
Aggarwal 2011 [122]	75	−ve	−ve	A&W 12 months
Ingle 2012 [123]	75	+ve	?	?
Dragoumis 2012 [124]	59	+ve	+ve	?
Ishida 2014 [124]	63	−ve	+ve	?

alive without recurrence one year later. The case reported by Gupta et al. was aged 75 with a 9.5 cm mixed mucoid cancer without nodal involvement treated by modified radical mastectomy [127]. The tumour was 60% mucoid, 40% IDC and ER/PR+ve, HER2−ve. These mixed mucinous carcinomas probably have a similar outcome to that of adenocarcinomas not otherwise specified.

Sarcoma

Breast sarcomas are regarded as rare tumours in women but in males the situation is but a microcosm of the female situation. Nevertheless in this world of miniature there is representation of the main sarcomas that have been described as part of FBC but with most descriptions being of single cases rather than series.

Phyllodes Tumour

In 1838 Johannes Muller reported several examples of unusual breast tumours which were bulky and showed rapid growth after several years of quiescence but with a benign nature and particular microscopic features. He called the lesion cystosarcoma phyllodes because he regarded it as being malignant. This work was cited by Lee and Pack in 1931 when they reported a series of 109 cases treated at the Memorial Hospital of whom 3 (3%) were males [128].

Phyllodes tumours are classified by the WHO as benign, borderline and malignant. The diagnostic criteria in terms of number of mitoses/10 high power field (hpf), margins, stromal overgrowth and stromal cellularity with atypia are outlined in Table 5.10. Radiologically, phyllodes tumours appear to have well defined margins and ultrasound suggests well-defined lobulated masses with posterior enhancement for both benign and malignant lesions.

Reingold et al. described a 54-year old male who had been aware of a painless right breast lump for >20 years [129]. Histology showed ductal proliferation with marked stromal cellularity associated with clefts and cysts. Because there was adjacent gynaecomastia it was postulated that endocrine changes leading to gynaecomastia were also responsible for the cystosarcoma phyllodes. Pantoja et al. treated a 70-year-old man whose breast lump had been present for 50 years [130]. The tumour was

Table 5.10 WHO classification of phyllodes tumours

Feature	Benign	Borderline	Malignant
Mitotic count/10 hpf	0–4	5–9	≥10
Margin	Pushing	Pushing or infiltrating	Infiltrating
Stromal overgrowth	Minimal/moderate	Moderate	Moderate/marked
Cell pleomorphism	Minimal	Moderate with atypia	Marked with atypia

treated by mastectomy with a skin graft. It weighed 8.6 kg, and histology showed it to be a malignant cystosarcoma with associated gynaecomastia. It was deemed to be the result of malignant transformation of a giant fibroadenoma.

Continuing with the theme of hyperestrogenisation being a driver of development of cystosarcoma, Johansson & Balldin reported a male treated with polyestradiol phosphate for prostatic carcinoma together with breast irradiation because of mastalgia [131]. He developed a malignant cystosarcoma phylloides. By 1987 when Nielsen and Andreasen described a case the nomenclature had changed to phyllodes tumour [132]. Their patient was a 71-year-old with bilateral gynaecomastia and a 4 cm left breast mass. Hormone assays showed elevation of plasma luteinising hormone (LH), prolactin and follicle stimulating hormone (FSH), but with normal free testosterone. Bartoli et al. reported a phyllodes tumor in a male who had taken estrogens for many years [133].

Hilton et al. performed a subcutaneous mastectomy on a 15-year old boy with a painless but enlarging left breast lump [134]. There was a 7 cm mass which histologically had a moderately pleomorphic stroma with occasional mitoses. Certain areas showed leaf-like projections typical of phyllodes. The diagnosis was regarded as being somewhere between a cellular fibroadenoma and a benign phyllodes tumour. Kahan et al. removed a 9.6 cm mass from the right breast of a 35-year-old man who had a small lump since childhood, but with rapid growth in the previous year [135]. One year after surgery he noticed a persistent lump and after 4 years re-excision was performed with clear margins. Subsequently he was treated with right breast irradiation (50Gy) and remained disease free after 5 years. He had liver disease and type II diabetes but his endocrine profile was normal except for an increase in sex hormone binding globulin (SHBG) leading to a reduction on free testosterone. The phyllodes tumour was of borderline malignancy and was ER/PR negative.

Campagnero et al. reported a 53-year-old African-American male with learning difficulties who had a 5 cm left breast lump which was shown mammographically to be a lobular density with associated coarse microcalcifications [136]. Core biopsy showed stromal fibrosis, ductal hyperplasia, and apocrine metaplasia, suggestive of phyllodes tumor. This was confirmed on excision biopsy so a left simple mastectomy was performed and he remained disease-free after 2 years. Konstantakos and Graham described a male with bilateral axillary phyllodes tumours [137].

Kim et al. described a 39 year-old male with a short history of a left breast lump [138]. He had a 1 cm mass with overlying skin thickening together with nipple retraction. There were no mammographic calcifications. Excision was performed and histology showed borderline phyllodes with gynaecomastia.

Angiosarcoma

Mansouri et al. reported of a 57-year-old man with primary angiosarcoma of the left breast treated by mastectomy who was alive 3 years later [139]. Granier et al. described yet another breast angiosarcoma in a 58-year-old man [140]. They regarded the standard treatment as being radical mastectomy associated with

adjuvant chemotherapy but few would now consider nodal surgery as having a role in the management of sarcomas. Wang et al. reported a 20 year old Chinese patient with an 18 cm breast mass [141]. Wide excision achieved clear margins but unfortunately the patient died of metastatic disease 6 months later. In a series of 154 angiosarcomas at various sites treated by the French Sarcoma group, 36 were male and their 5 year survival was 43% compared with 45% for the females [142]. Kamat et al. described a 57 year-old male who was HIV+ve and presented with a 12 mm breast lump which was hypoechoic on ultrasound [143]. Core biopsies showed angiosarcoma and after normal staging investigations he underwent total mastectomy for what proved to be a low grade angiosarcoma. No follow up information was available.

Liposarcoma

Huebert reported 104 cases of liposarcoma at various sites registered in Manitoba between 1944 and 1978 and of these 59 (57%) were male [144]. The 10-year overall survival was 49%, better in those who had surgery and unaffected by radiotherapy. Sezer et al. described a 70 year-old male with a painless enlarging left breast lump [145]. Ultrasound showed a heterogeneously echogenic well-defined mass. Contrast-enhanced (CT) scan revealed a large subcutaneous tumour arising from the pectoralis major muscle. This was excised and proved to be a pleomorphic liposarcomas. He received postoperative radiotherapy and was disease-free 9 months later.

Raj et al. described a 66-year-old male who presented with an enlarging right breast lump at the site of prior trauma [146]. Mammography and ultrasound showed breast and axillary masses and a core biopsy suggested fibromatosis. Because the imaging features were suggestive of malignancy he underwent radical mastectomy. The specimen was reported as dedifferentiated liposarcomas. Subsequently he received adjuvant chemotherapy and radiotherapy. Pasta et al. treated a 69 year-old man with breast liposarcoma by mastectomy followed by chemotherapy and radiotherapy [147]. He remained disease-free 4 years later.

Fibrosarcoma

In a series of breast sarcomas treated at Sloan Kettering Memorial, one was a 50 year-old male with a fibrosarcoma [148]. He was treated by radical mastectomy and died without recurrence 15 years later. Kidmas et al. reported two cases of Nigerian male breast fibrosarcomas and both patients were treated by modified radical mastectomy [149]. No follow-up data were available. Shukla et al. described a 28-year-old male who had a right breast lump for 7 years before diagnosis but which had recently increased in size [150]. The lump was 10 cm and mobile and FNAC suggested spindle cell sarcoma. He underwent radical mastectomy and histology showed interlacing spindle shaped cells with a herring bone pattern and foci of

myxoid change and 1 mitosis per10 high powered fields. A grade I primary fibrosarcoma was diagnosed and the patient was alive without recurrence one year later.

Malignant Fibrous Histiocytoma (MFH)

This malignancy was first described by O'Brien and Stout in 1964 and they called it malignant fibrous xanthoma [151]. Of the 21 cases, 4 MFH were located within the breast and one patient was a 70 year-old male. He was treated by wide excision and was well without recurrence more than 6 years later. Mahalingam et al. reported a 71-year-old African American male with a rapidly increasing painless left breast lump [152]. There was a mobile lump with no overlying skin changes and ultrasound showed a solid lobulated 3 cm mass. FNAC revealed malignant cells with a background of inflammation and fibrosis. He underwent total mastectomy after a frozen section diagnosed MFH. Three years later he was alive without recurrence.

Hartel et al. reported 19 cases of primary breast MFH and one of these was male [153]. IHC showed demonstrated expression of CD68 (71%), focal smooth muscle actin (36%), and only rarely ER and PR positivity. All cases were negative for CD34, S-100 protein, desmin 33, and keratins, including CK7, CK20, CK5/6, and CK18. Of 15 patients with follow-up data, 5 (33% overall) died of metastatic disease within 7 months after diagnosis.

Dermatofibrosarcoma Protuberans

Dermatofibrosarcoma protuberans (DFSP) is a rare and locally invasive skin tumor found most frequently on the trunk and proximal extremities of young adult males. The first reported case affecting the breast was a 41-year-old Chinese man who initially presented with a right-sided lump [154]. Mammography showed two masses, the larger well-defined and the other irregular. Breast MRI was performed and on T1-weighted imaging, both masses showed decreased signal compared with to fat and slightly increased signal in relation to pectoralis major. Both lesions were more intense than fat on T2-weighted imaging. The larger lump was well defined and there was a distinct rim of decreased intensity between it and the fat interface. The smaller lump was less well defined border on standard T2 weighted images but after fat-suppression both lesions had clearer borders with a slight mass effect of the larger lump on the underlying pectoralis major. After wide excision histology showed highly cellular monomorphic slender spindle cells in a cartwheel (storiform) pattern aligned at right angles to vessels. As the spindle cell nuclei were well differentiated and there were infrequent mitoses the diagnosis of DFSP was made.

Table 5.11 Male cases of breast dermatofibrosarcoma protuberans

Author	Patient age	Tumour size	Outcome
Chen 2009 [154]	41	4.5	?
Park 2011 [155]	36	–	?
Akhtar 2012 [156]	22	5	?
Prabhu 2014 [157]	55	5	?
Al Tarakji 2015 [158]	27	4	Alive 1 year
Saikia 2016 [159]	40	4.5	?

Subsequent cases of DFSP are summarised in Table 5.11 [154–159]. This indicates the relatively young age at presentation. Unfortunately, yet again there have been no long-term reports of outcome. The most important aspect of management is to achieve clear surgical margins in order to minimise risk of local recurrence.

Osteogenic Sarcoma

Ostogenic sarcomas arising within the breast are exceedingly rare and need to be distiguished from metaplastic change in pre-existing benign or malignant lesions such as phyllodes tumours. Silver and Tavasolli reviewed 50 breast osteosarcomas of the breast, diagnosed between 1957 and 1995, and of these only one patient was male [160]. Lack of epithelial differentiation was confirmed with a panel of immune-histochemical markers. No evidence of axillary nodal involvement was found and of those cases with follow-up information, 41% had died after an average of 17 months. Recommended treatment was wide excision or mastectomy without axillary surgery.

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Chapter 6
Molecular Profile

Abstract Examination and comparison of MBC and FBC at a molecular level reveals striking and potentially exploitable differences. Over 90% of MBC are ER+ve compared with approximately 70% of FBC. Androgen receptor mutations may be responsible for occasional MBC cases but for the majority no clear link has been shown. MIB1 is not of prognostic significance in MBC, nor is bcl2 expression. The molecular subtypes of MBC are predominantly luminal A, sometimes luminal B, rarely basal and very rarely HER2. Two MBC genomic subgroups have been described: male-complex and male-simple and the latter appears to be a male specific type. The Oncotype DX test may be useful in determining likely prognosis and suitability for chemotherapy in node negative MBC. Overexpression of cell cycle proteins such as cyclin-D and c-myc is associated with reduced lymphatic involvement and longer disease-free survival. Assembly of tissue banks of MBC will enable a greater understanding of the molecular profile and open the door to new specific therapies.

To see what is in front of one's nose needs a constant struggle. George Orwell

Introduction

Instead of having to rely on morphological features demonstrated after staining with haematoxylin and eosin (H & E), molecular biology has yielded a panel of reagents for immunohistochemistry (IHC) to enhance the characterisation of tumours. This has not only improved diagnostic precision but also led to more sophisticated prognostic markers.

Estrogen and Progesterone Receptors

The pioneering work of Jensen which led to the identification of estrogen receptor (estrophilin) in 1960 enabled a rational approach to the endocrine treatment of breast cancer [1]. This was followed by O'Malley's characterisation of the

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progesterone receptor in 1970 [2]. After being used widely to select therapies for FBC, Leclercq analysed 11 MBC samples, 7 primary and 4 metastatic for cytoplasmic estrogen receptors [3]. They measured the binding affinity of cytosol fractions for 3H-17βestradiol and the dissociation constants of binding were within the range reported for FBC. When present, receptor concentrations varied from 59 to 532 femtomoles/mg tissue protein. Competition studies indicated that the receptors were specific for estrogens and anti-estrogens suggesting that estrogen receptor (ER) was identical in MBC and FBC.

Rosen et al. assayed ER in specimens from 3 MBC cases and all were ER +ve with concentrations of 10, 16 and 105 fmoles/mg of cytosol protein [4]. Larger studies followed with Everson et al. reporting ER positivity in 29/34 (85%) of MBC cases [5]. Andres et al. investigated ER, PR, HER-2/neu and EGF-receptor status in 98 MBC specimens and found that 82 (84%) were ER+ve and 78 (80%) PR+ve [6]. The ER and PR protein levels were higher in males than females. In Cutuli's large French MBC series ER was measured in 419 tumours and was positive in 385 (92%) and analysis for PR was positive in 356/399 (89%) [7]. Within the series the receptor phenotype was: ER+ve PR+ve (86%), ER+ve PR−ve (6%), ER−ve PR+ve (3%) and ER−ve PR−ve (5%).

Androgen Receptor

Part of our problem understanding the molecular biology of MBC is the absence of cell lines. There is in contrast a plethora of FBC established cell lines which have acted as substrates for extensive research and in particular, study of endocrine modulation of behaviour *in vitro*. The androgen receptor (AR) is activated by binding to testosterone or dihydrotestosterone and the complex translocates to the nucleus. Its role in MBC has been the subject of great interest and frequent disappointments.

In 1992, Wooster et al. reported two brothers with MBC and both had clinical and endocrine evidence of androgen resistance (Reifenstein syndrome) [8]. After sequencing they found a mutated AR gene within the region encoding the DNA binding domain on the X chromosome. Subsequently Lobacarro et al. screened 13 MBC tumours for the presence of germline mutations in exons 2 and 3 encoding the DNA-binding domain of the androgen receptor [9]. In one of these thirteen patients, single strand conformation polymorphism and direct sequencing detected a guanine-adenine point mutation at nucleotide 2185 that changed Arg608 into Lys in the second zinc finger of the androgen receptor. This mutation was found in a 38 year old male with partial androgen insensitivity syndrome but normal androgen-binding. The authors postulated that the androgen receptor mutation might invalidate the protective effect of androgens on male breast tissue.

Syrjäkoski et al. screened the entire coding region of the AR gene for mutations and also studied the role of repeat lengths of AR CAG and GGC in cancers from 32 Finnish MBC cases [10]. They did not find any germ-line mutations and CAG and

Table 6.1 Frequency of AR positivity in MBC

Author	N	AR+ve
Sasano 1996 [11]	15	13 (87%)
Rayson 1998 [12]	77	73 (95%)
Munoz de Toro 1998 [13]	13	5 (39%)
Pich 1999 [14]	47	16 (34%)
Kidwai 2003 [15]	26	21 (81%)
Kwiatowska 2003 [17]	39	15 (38%)
Murphy 2006 [18]	16	14 (87%)
Sas-Korczynska 2015 [19]	32	20 (62.5%)

GGC repeat lengths were similar in cases and controls so they concluded that the AR gene mutations were not a major influence on MBC risk.

Those studies measuring AR in MBC are outlined in Table 6.1 which indicates the heterogeneity of the findings [11–18]. The likelihood is that these differences are methodological but at present it is difficult to draw conclusions as to the relevance of AR expression in MBC.

Rayson et al. measured androgen receptors in 77 tumours from a cohort of 111 MBC patients treated at the Mayo Clinic between 1950 and 1992 at the Mayo Clinic and 95% of these were AR positive [12]. Because of this high positivity they were unable to assess whether AR had any influence on prognosis. In contrast, Kwiatkowska et al. reported that AR positivity was adversely associated with 5-year survival in a series of 43 MBC cases (AR+ve 33% versus 74% AR−ve [17]. Wenhui et al. provided corroborative data having measured AR, ER, PR, HER2 and Ki-67 (MKI67)) in specimens from 102 Chinese MBC cases [20]. High levels of AR expression were associated with axillary nodal spread and a significantly reduced 5-year overall By contrast. There was improved overall survival those AR-negative patients given adjuvant tamoxifen therapy.

In contrast, when Sas-Korczyska et al. performed androgen receptor assays in 32 specimens they reported that AR expression was present 20 (63%) and more frequently expressed in 17/20 (85%) of ER+ve tumours [19]. Tumours that were AR−ve were associated with a worse 5 year survival (30% versus 52%),

Johannson et al. analysed 56 fresh frozen MBC specimens using high-resolution tiling BAC arrays and compared the pattern of expression with a genomic data set of 359 FBC [21]. There was a broad spectrum of aberrations indicating the heterogeneity of MBC with genomic gains being more frequent in MBC compared with FBC but with fewer genomic losses of material. They suggested two MBC genomic subgroups called male-complex and male-simple. The male-complex type was similar to the luminal-complex FBC subgroup, whereas the male-simple appeared to be a male specific type. There are many similarities between FBC and MBC with respect to genomic imbalances, but also distinct differences as revealed by high-resolution genomic profiling. MBC can be divided into two comprehensive genomic subgroups, which may be of prognostic value. The male-simple subgroup appears notably different from any genomic subgroup so far defined in FBC.

Callari et al. surveyed the transcriptomic landscape of MBC and compared the gene expression profiles of 37 ER+ MBC biopsies with 53 ER+ FBC specimens of similar histology [22]. There were almost a thousand genes expressed differently in MBC and FBC suggesting that gender plays a major role in key functions including energy metabolism, translation regulation, and matrix remodelling together with immune system recruitment. Furthermore the analysis of genes associated with steroid receptors indicated the likelihood of a major role for AR in MBC with breast cancer being a very different phenomenon in male and females with the potential for exploitation of those differences for therapeutic purposes.

Ki67/MIB-1

Ki67 is a monoclonal antibody which detects a nuclear antigen expressed in proliferating cells but can only be used on fresh frozen specimens. In contrast the monoclonal antibody MIB-1 which identifies recombinant components of Ki67 antigen can be used to measure proliferation in archival formalin-fixed and paraffin-embedded tissue. Pich et al. analysed 27 MBC specimens using MIB1 and allocated a score based upon the proportion of malignant cells staining with the antibody [23]. The mean MIB-1 score was 23.76% and staining was present only in the cell nuclei. There was no association between MIB-1 score and grade, stage, or ER / PR status. Those cases with a MIB-1 score $\leq$23.5% had a median survival of 73 months compared with 37 months for those with scores >23.5% (P = 0.01).

Wilsher et al. determined MIB-1 expression in 41 MBC and reported that 40% were positive [24]. Rayson et al. carried out IHC on 77 MBC specimens and taking a cut-off of $\geq$20% of cells staining, 48 (62%) were negative and 29 (38%) positive. The 5 year progression free survival was significantly worse in the MIB-1+ve cases, 48% versus 80% (p = 0.012). In contrast a series of 41 MBC cases from Kuwait were reported to have 100% Ki67 staining [25]. Wang-Rodriguez et al. examined tumour blocks from 65 MBC cases and used immunohistochemistry to determine ER, PR, p53, Her2-neu, and MiB-1 status [26]. As controls they used gynaecomastia specimens from 17 age-matched cases. Their threshold for MIB-1 positivity was >10.6% and on this basis 19 (29%) of the MBC were positive. All the gynaecomastia controls were MIB-1 negative. There was no relationship between MiB-1 expression and survival, and they concluded that MIB-1 expression was of limited value in MBC.

Kanthan et al. examined specimens from 75 cases of MBC for IHC expression of many variables including Ki67 and cyclin-D1 clinico-pathological variables such as tumor size, stage, nodal status and disease free survival (DFS) [27]. The MBC cases were predominantly MIB-1 negative. There was no relationship between MIB-1 status and tumour stage or disease-free survival leading the investigators to conclude that MIB1 does not play a major role in the behaviour of MBC. Kornegoor et al. carried out IHC on specimens from a large Dutch series of MBC, including MIB-1 among the panel of antibodies [28]. MIB-1 positivity was found in 24/131 (18%) of the tumours. Among the grade III cancers there was significant over-expression of MIB-1. There was no significant association between MIB-1 status and outcome.

Further confirmation of the lack of prognostic significance of MIB-1 status came from the work of Schildhaus et al. [29]. Of the 92 MBC tumour microarrays that they analysed 69 (75%) were negative. Although the Ki67 cases had a shorter median overall survival, 48 versus 102 months, this did not achieve statistical significance. Using a 20% cell staining threshold for positivity, Gargiulo et al. reported that 22/34 (65%) of MBC cases were MIB-1 positive [30]. Again, this was not significantly associated with survival. Despite sometimes varying percentages of MIB-1 expression, all the recent publications suggest that MIB-1 is not an important variable for determining prognosis in MBC.

Bcl2

Bcl-2 (B-cell lymphoma 2) is the product of the *Bcl2* gene and is an anti-apoptotic protein. Weber-Chappuis et al. compared expression of tumour markers in 66 MBC and 190 histologically matched FBC [30]. There was a high percentage of *bcl-2*+ve tumours among the MBC. In the Mayo Clinic series of 111 MBC cases, there was expression of *bcl2* in 104 (94%) [12]. Among the 41 MBC cases reported by Temmim there was bcl2 positivity in 32 (78%) [25]. After Abdel-Fatah et al. had shown that the combination of bcl2 and mitotic index identified significantly different prognostic groups in FBC [31], Lacle revisited this relationship in a series of 151 MBC [32]. Of the MBC cases, 142 (94%) expressed *Bcl2* and this was unrelated to tumour size, grade or mitotic index. The combination of *Bcl2*/mitotic index was not a prognostic indicator for MBC.

Molecular Subtypes

Sorlie et al. examined patterns of expression of 534 intrinsic genes using hierarchical clustering in 115 female breast cancers [33]. Four groups emerged: luminal A (43%), luminal B (20%), HER2 (10%) and basal (46%). Subsequent analyses of MBC revealed a very different spectrum of molecular subtypes. In a large multicentre investigation, Shaaban et al. examined the receptor profiles of tumours from 251 MBC and 263 FBC which had been matched by tumour grade, patient age, and nodal status [34]. The most common phenotype was Luminal A in both MBC and FBC. No luminal B or HER2 phenotypes were seen in MBC and basal phenotype was rare in both. Hierarchical clustering showed that whereas in FBC estrogen receptor alpha (ERα) clustered with progesterone receptor (PR); in MBC, the clustering was of ERα, estrogen receptor beta (ERβ) and androgen receptor (AR).

Further conformation came from the study by Kornegor et al. who analysed 134 cases of MBC by immunohistochemistry (ER, PR, HER2, EGFR, CK5/6, CK14 and Ki67) [28]. Of the cases, 75% were luminal A, 21% luminal B and the remainder were either basal type (4) or unclassifiable triple negative (1). Nilsson et al. reviewed tumours from 197 MBC patients and performed immunohistochemistry

(IHC) on tissue microarrays and histological grading using conventional slides [35]. Most were ER positive (93%) and PR positive (77%) but only 11% were HER2 positive. Nottingham histological grade (NHG) III was seen in 41% and HER2 positivity in 11%.

Using IHC results to classify the tumours into molecular subtypes based on 5 biomarkers (ER, PR, HER2, CK5/6 and EGFR) revealed luminal A and luminal B in 81% vs. 11%. There were two cases of basal-like cancer but no cases of HER2-like tumour. There was no difference in breast cancer mortality between the luminal subgroups suggesting the prognostic impact of molecular subtyping in MBC differs from that in FBC.

The combined results of these series are summarised in Table 6.2 [28, 29, 35–39]. For comparison with FBC the data reported by Inwald et al. on over 4000 FBC cases from the Regensburg Cancer Registry are shown. There are major differences with luminal A being the predominant subtype in MBC with minimal numbers of basal cell types and no HER2 enriched subtype being seen in males.

Plasilova et al. determined the TN status of both FBC and MBC cases diagnosed between 2010 and 2011 and registered with the National Cancer Data Base (NCDB) [40]. Of 295,801 FBC, 38,628 (13%) had TN tumours compared with 185/3136 (6%) MBC cases. The highest incidence was seen in African-Americans (24%), and the lowest in Filipinos (9%). Taken together, the molecular profiles indicate that FBC and MBC are very different diseases with HER2 subtype being very rare in MBC and basal types representing only 2% of male cases (Table 6.3).

Table 6.2 MIB1 status and outcome in MBC

Author	N	MIB1 +ve	Outcome
Pich 1994 [23]	27		+ve worse OS
Wilsher 1997 [24]	41	40%	–
Rayson 1998 [12]	77	38%	+ve worse 5 years PFS
Temmim 2001 [25]	41	100%	–
Wang-Rodriguez 2002 [26]	65	29%	No effect
Kanthan 2010 [27]	75	20%	No effect
Kornegoor 2012 [28]	131	18%	No effect
Schildhaus 2013 [29]	92	25%	No effect
Gargiulo 2016 [30]	34	65%	No effect

Table 6.3 Molecular profile of MBC and FBC

Author	N	Luminal A	Luminal B	HER2	Basal
Ge 2009 [37]	42	35 (83%)	7 (17%)	0	0
Shabaan 2012 [35]	251	246 (98%)	0	0	5 (2%)
Kornegoor 2012 [28]	134	100 (75%)	28 (21%)	0	4 (4%)
Nilsson 2013 [36]	183	160 (87%)	21 (11%)	0	2 (1%)
Schildhaus 2013 [29]	96	56 (58%)	37 (39%)	0	3 (3%)
Abreu 2016 [38]	111	99 (89%)	8 (7%)	1 (15)	3 (3%)
FBC (Inwald 2015) [39]	4344	2102 (48%)	1078 (25%)	774 (18%)	390(9%)

Cell Cycle Proteins

The cell cycle comprises four phases, gap 1 (G1), synthesis (S), mitosis (M) and gap 2 (G2). Within the cycle there are three major checkpoints, G1 (verification of growth and environmental suitability for DNA synthesis, G2 (check on DNA synthesis and conditions for cell division) and finally metaphase (checking chromosome alignment on the spindle). Kanthan et al. used IHC to classify 75 MBC cases, examining expression of proliferating cell nuclear antigen (PCNA), Ki67, p16, p21, p27, p57, cyclin-D1 and c-myc [27]. PCNA is a DNA clamp, anchoring DNA proliferation and repair proteins and was over-expressed in 98% of cases. Ki67 is a nuclear marker present throughout the cycle but elevated under conditions of cell proliferation but was negative in 78% of MBC specimens. p16, p21, p27, p57 are all inhibitors of cyclin dependent kinases (CDKN1) and act as brakes on cell proliferation. p16 was expressed in 77%, p21 in 41%, p27 in 81% and p57 in 59%. Cyclins regulate G1-S phase transition which is shortened when cyclin D1 is induced and over-expression was observed in 84% of MBC cases. C-myc protein binds to DNA, enabling transcription of cyclin-dependent kinases and was expressed in 90% of MBC cases. These results are shown schematically with black blocks showing expression in Fig. 6.1.

With regards to prognosis, there was reduced disease-free survival (DFS) in the overexpressing tumours and this was inversely correlated with Ki67 expression of which was predominantly negative (78.3%). Cyclin D1 positive tumours tended to be with a lower incidence of lymph node involvement and an increased DFS of >150 months ($p = 0.04$). Overexpression of c-myc (90%) was associated with less nodal disease and increased DFS. Over-expression of p16 did not significantly affect DFS but this was reduced in those with tumours overexpressing p21 and p57.

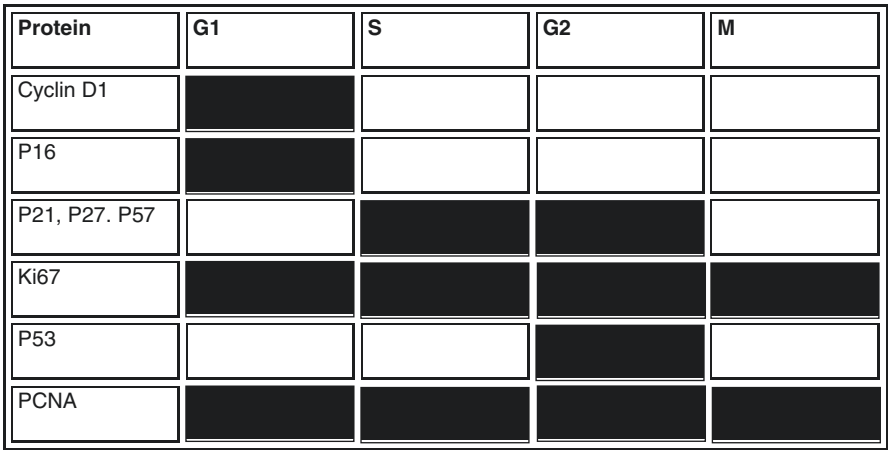

Fig. 6.1 Expression of cell cycle proteins during cell cycle (Kanthan 2010)

Oncotype DX™

Oncotype DX measures expression of 21 genes by reverse transcriptase polymerase chain reaction in RNA extracted from archival specimens. The test uses 16 cancer-associated genes and 5 reference genes and assigns a recurrence score, RS (low risk score<18, intermediate risk ≥18–<31, high risk ≥31). Paik et al. analysed 668 tumours from women who participated in NSABP B14 trial in which women with node negative estrogen receptor positive breast cancer were randomised to tamoxifen or placebo [41]. Ten year distant recurrence rate for the low risk group was 7% compared with 14% in the intermediate group and 31% in the high risk group. In multivariate analysis oncotype DX yielded prognostic power independent of tumour size and grade. Not only did it predict overall survival for the group but being a continuous variable was indicative of individual risk.

Henry et al. conducted Oncotype DX assays on tumours from 29 patients with breast cancer, including one case of MBC [42]. They sought to determine the impact of the test on medical oncologists' recommendations regarding adjuvant chemotherapy. For the male patient the eventual recommendation changed from no to yes. In a review of treatment for 73 MBC cases Kiluk et al. reported that three of the recent patients met the criteria for Oncotype Dx testing [43]. Of these, two had intermediate RS and were advised to receive chemotherapy. The other MBC case had a low RS and was treated with endocrine therapy without chemotherapy.

Following this Grenader et al. measured RS distribution in 65 Israeli male breast cancer (MBC) patients [44]. Of the patients 29 (45%) were low risk, 27 (42%) intermediate and 9 (13.9%) high risk. This distribution of recurrence risk groups was similar to that in 2455 female tumours assayed during the same time period. Yokoyama et al. used oncotype DX to determine treatment for 60-year-old man was diagnosed with stage I breast cancer. Surgery comprised mastectomy and sentinel node biopsy followed by axillary clearance because of a micrometastasis. The tumour was tested with oncotype DX which indicated a recurrence score of 8 (low recurrence risk) so he was treated with endocrine therapy and spared adjuvant chemotherapy. It will require national and international trials to confirm the role for Oncotype-DX in MBC but until that time a pragmatic acceptance would appear to be the best policy.

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Chapter 7
Psychosocial

Abstract With a relatively small body of evidence, conclusions concerning the psychological aspects of MBC need to be tentative. Few men consider themselves as increased risk but those who have *BRCA* mutations may suffer guilt and isolation. The main reasons for seeking genetic testing concerns risk for other family members. Despite recommended criteria for testing only a quarter of eligible cases are referred. It appears that levels of anxiety and depression following diagnosis of breast cancer are substantially lower in men than in women. High levels of cancer-specific distress occur in a quarter of cases. Compared with FBC patients, males report higher scores in terms of physical function, role function, pain, energy, sociability, and mental health but in relation to the general male population suffer significantly worse psychological and physical function. Males may feel isolated and unable to obtain the relevant information from those who are caring for them in the breast team. The internet does have several websites dealing with MBC issues but this cannot replace the need for good communication at a personal and local level.

Fere libenter homines id quod volunt credunt
Men are nearly always willing to believe what they wish. Julius Caesar

Introduction

In contrast with the industrial scale of investigations into psychosocial aspects of female breast cancer, studies on MBC are still at the level of a cottage industry. Nevertheless this vacuum is now becoming gradually occupied by more rigorous, statistically robust evidence that will enable a holistic approach to the needs of men with breast cancer. Studies have largely examined two aspects: assessment and management of risk together with psychosocial aspects of the diagnosis and treatment of MBC.

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Risk

The majority of males will not consider themselves at risk of MBC but with increasingly sophisticated genetic screening a target group can be identified. A Canadian study assessed 59 male carriers of *BRCA1/2* mutations to determine their reasons for asking for counselling and testing [1]. Additionally the extent of family involvement, subjective risk perception, participation in screening and patient satisfaction was sought.

What emerged was that the main reason for wanting counselling was concern about their daughters' risk of breast cancer. The majority, 88%, had discussed breast and ovarian cancer with their family and almost half, 47%, had considered prophylactic surgery. Despite believing that they were at increased risk of development of cancers of the prostate, breast, colon and skin only 43% changed the pattern of prostate screening after being told that they were carriers of a pathological mutation. As a result, 55% suffered intrusive thoughts about developing cancer in the future. The authors stressed that there was inadequate information about men's experiences available to the medical profession.

Strømsvik et al. interviewed 15 Norwegian *BRCA1/2* males and in the first interview they were seen alone and in the second, 7 attended with female partners [2]. On being told they were mutation carriers all the men admitted to having major emotional reactions including fear of malignancy and guilt because they deemed themselves responsible for putting their offspring at risk. Partly because of this they wished to keep this information private. They were unable to discuss the situation with other men and turned to females for support. The lack of social support meant that they were psychologically vulnerable.

To examine the extent and nature of disseminating results of BRCA1/2 testing to offspring Hallowell et al. questioned 17 MBC patients, 8 partners and 4 adult children [3]. The interviews examined the experiences of cancer and genetic testing, reasons for undergoing genetic testing and communication of results and to the immediate family. In terms of the latter both MBC patients and their partners felt it was their responsibility, rather than that of the doctors, to inform their children of the results. This could be complete disclosure, limited communication or total secrecy based on their perception of children's rights and parental wish to shield their children from potentially angst-provoking information.

In an examination of perceptions about MBC, 36 Malayan male university students who had been randomly selected were interviewed [4]. Most were aware of a low risk of MBC but believed that the major cause was cigarette smoking. Although the majority would urge family members to practice breast self-examination this was deemed unimportant in men because of the low risk. This indicated that even among intelligent university students there were major misconceptions about the cause and early detection of MBC.

Hesse Biber conducted an online survey of 101 men who had been found to be *BRCA* mutation carriers [5]. A subset of 26 participated in an in-depth interview including a Genetic Testing Motivation Scale, together with the Bem Sex Role

Inventory (BSRI). The sample was predominantly white (96%) and upper/middle class (87%). The main reason for seeking genetic testing was family risk for 45 (70%), medical considerations in 14 (22%) and social support for 5 (8%). Men who were aged ≤50, or without children, were more likely to give medical reasons for their choice. With regard to perception of stigmatisation, this occurred more frequently in those aged ≤50. Vulnerability was more likely in married men and working professionals were more worried than the retired.

The situation may be worsened by inertia within medical organisations. Chun et al. examined compliance with the recommendations for genetic testing issued by the National Comprehensive Cancer Network (NCCN) within the Veterans Administration (VA) in the US [6]. Using the VA Central Cancer Registry together with details of *BRCA* test orders from Myriad Genetics, they found that, of the 462 Veterans who met NCCN criteria, only 126 (27%) were referred for counselling or testing. Of the 98 VA Medical Centres, there were no referrals for genetic testing from 49 (50%). Furthermore those cases with second primary cancers were even less likely to be referred for counselling or testing.

Post-diagnosis Problems

In 1991, John W Nick died of metastatic MBC and subsequently his daughter set up the John W Nick Foundation (www.malebreastcancer.org). The aim of the Foundation is to increase awareness of breast cancer in men. This was the first attempt to provide an accessible on-line resource specifically aimed at MBC. At that time the psychological aspects of such a diagnosis were largely unexplored.

In a small pilot study from Wales, 6 MBC patients took part in in-depth interviews which although unstructured nevertheless focussed on the physical and psychological impact of the diagnosis and treatment [7]. Interviews took place in the patients' homes with or without the presence of a partner who was encouraged to participate. Seven major concerns emerged: delay, shock, stigma, body image, causal factors, information paucity and lack of emotional support. This work was expanded into four focus group discussions with 27 participants with MBC and FBC, together with Healthcare professionals [8]. After recording and transcribing the discussions were examined by thematic analysis which yielded four major themes: diagnosis, disclosure, support and male-based information. In this study, delay had not been an issue but there was some stereotyping by health professionals who deemed men to act stoically when given the diagnosis whereas females were more emotional. Possibly as a result of self-selection, disclosure was not a problem for the participating males although some did not reveal their scars in public. Most of the support came from partners and the men did not want specific MBC information but rather an incorporation of male-relevant information into FBC factsheets.

The same group then went on to administer cross-sectional questionnaires to 161 MBC cases [9]. Questionnaires including HADS (Hospital Anxiety and

Depression Scale), IES15 (Impact of Events Scale), BIS (body image scale), COPE42 (coping) and stress appraisal in relation to activity, appearance and pain. Clinically treatable levels of anxiety were reported by 6% but only 1% had depression. High levels of cancer-associated distress were reported by 23%. Anxiety was mostly associated with fear about the future whereas symptoms of depression were largely the result of altered body image. Body image, avoidance coping, uncertainty, and lack of gender-specific information were major contributors to cancer-related distress.

The sense of anxiety and isolation was exemplified in a case report from Smolin and Massies [10]. Mr. T noticed right nipple retraction but was reassured by his doctor. One year later another doctor referred him to a surgeon and he underwent right modified radical mastectomy for a 3 cm invasive cancer with 7/25 nodes involved. The tumour was CER/PR positive and he received adjuvant chemotherapy, adriamycin, cyclophosphamide, paclitaxel and cisplatin, followed by tamoxifen. This was followed by a stem-cell transplant after which he was referred by the medical oncologist for a psychiatric opinion because of his fear of recurrence.

He gave a long history of anxiety and depression which had been particularly severe when his mother died of breast cancer and worsened by his father's subsequent re-marriage. He had dropped out of university but had several reasonably rewarding jobs although he had always been insecure feeling that "the bottom might fall out at any time". He had a twin brother and a girlfriend but the relationship was described as conflictual although both had given support during his treatment. A diagnosis of adjustment disorder with mixed emotion was made and he was referred for psychotherapy which took place 3–4 times monthly and concentrated on helping him to adjust and have a more fulfilling existence. During the first year, because of side effects of tamoxifen - depression, loss of libido and leg cramps he had temporarily discontinued but the situation improved when the dosage was reduced to 10 mg daily. During the second year he was more compliant with treatment and following a financial windfall his concerns shifted from fear of recurrence to concern about other aspects of life including expansion of his business, a desire to marry and the possibility of breast reconstruction. The authors considered that his reactions to the diagnosis were similar to those of younger single women with breast cancer.

Applying a different approach, Donovan and Flynn, using semi-structured interviews conducted a phenomenological analysis of what was called the "lived experience" (AKA "life") of 5 MBC cases [11]. Partly as a result of inaccurate perception and inadequate communication from health professionals, they described an underlying feeling of stigmatisation and loss of masculinity.

The US 2009 Behavioral Risk Factor Surveillance System (BRFSS) collected information by random digit dialling [12]. Using data from this source Androwski conducted a case control study with 66 MBC cases and 198 controls matched for age, gender and ethnicity. The aim was to examine physical and mental well-being together with aspects of lifestyle. Among the items collected were height and

Table 7.1 Behavioural variables of MBC cases and controls (Androwski 2011) [12]

Variable	MBC	Controls
Life satisfaction	1.78*	1.53
Support	1.84	1.95
Poor physical health days in past month	6.45	3.81
Poor mental health days in past month	4.83*	1.56
General health rating	3.15	2.70
Poor sleep days in past month	8.90	5.60
Co-morbidity	2.67*	1.88
Body mass index	29.21	27.72

*$P < 0.05$

weight, together with general health which was self-rated on a 5 point scale ranging from "poor" to "excellent". Social and emotional support was rated in terms of frequency on a 5 point scale from always to never and satisfaction with life in four grades from "very dissatisfied" to "very satisfied". Higher values represented poorer life satisfaction, less support and poorer health.

In addition to the matching the two groups were also similar in terms of partner status, education, employment and income. Results are summarised in Table 7.1. Cases were more likely to be obese and carried a heavier burden of co-morbidity including diabetes, heart attack, asthma and arthritis. Life satisfaction was significantly reduced among the MBC cases who were also more likely to report that in the past 30 days they had more days in which their mental health had not been good. These sequelae could not be definitely ascribed to the diagnosis of MBC but since the average interval between diagnosis and telephone interview was 12 years this suggested a long-standing effect.

Health-related quality of life (HRQoL) in German MBC patients was investigated by Kowalski et al. From a total of 20,673 breast cancer patients who completed the HRQoL (SF-36) questionnaire there were 84 MBC cases. The HRQoL scores of male breast cancer patients were compared with reference populations. In comparison with FBC patients, males reported higher scores in terms of physical function, role function, pain, energy, sociability, and mental health. In contrast, in relation to the general male population, MBC patients achieved lower scores in SF-36 subscales and they suffered significantly worse psychological and physical function.

Ruddy et al. recruited 42 MBC cases to an online survey which included the expanded prostate cancer index composite (EPIC) scale, Hospital Anxiety and Depression Scale (HADS), and the 37 item Functional Assessment of Cancer Therapy-Breast (FACT-B) Index [13]. In terms of the EPIC Sexual subscale, 40% of MBC cases reported that their sexual function had been very poor during the previous month. The EPIC hormonal score was based on hot flushes, mastalgia, depression, weight loss and energy levels during the previous 4 weeks. With a mean score of 85 (range 45–100) with lower scores denoting more symptoms this indicates that hormonal side effects, including mood change/depression were an

important problem. There did not appear to be a significant difference in EPIC hormonal scores between those taking and not taking endocrine therapy. With a mean FACT-B score of 111.1, this indicated poorer quality of life in MBC patients.

Following this the Dana-Farber Cancer Institute set up an MBC telephone support group which was toll-free and with coded access [14]. Sessions took place at noon and were facilitated by a dedicated social worker with occasional input from a sexual health expert and a medical oncologist. Six months after the final meeting participants were asked for feedback with regard to the helpfulness of this approach. The response rate was 72% and three quarters of participants found the sessions useful or very helpful because they gained information and met others with the same problem. When asked whether they would recommend an online help facility to others with MBC, 90% answered in the affirmative.

Kipling et al. carried out a survey on 78 men who attended a One-Stop Clinic over an 18 month period [15]. The majority had gynaecomastia and only one had malignancy which was DCIS. The questions included length of symptoms (mean 6.7 months), age (range 18–78), preference for an all-male clinic with a longer wait (1%) and satisfaction with their clinic experience (good/excellent 100%). Of those surveyed 37% described negative feelings relating to their condition although they did not want to be seen in an all-male breast assessment clinic if that meant a longer wait. The authors concluded that men in Durham did not want all-male assessment clinics.

Quincey et al. reviewed the experiential literature on MBC and concluded that there was often marginalisation of these cases leading to multiple psychosocial and psychosexual problems over and above those resulting from local and systemic therapy [16]. They asserted that the pink ribbon symbol of Breast Cancer Awareness could have a possible potentially alienating and emasculating effect on men with the disease and "pinkification" should be phased out.

In a study from Johannesburg, RSA, Rayne et al. examined whether a diagnosis of MBC affected the perception of masculinity for patients [17]. A case-note review of 23 patients was followed by a telephone survey completed by 18. The majority (17/18) of those interviewed had told relatives and friends of the diagnosis. They were asked whether they were aware of the existence of MBC before they were diagnosed. Overall 33% answered yes but none of those who were black were aware of MBC. Of those who went to government hospitals, only 11% were MBC-aware and only 33% of those aged >65 were aware. Of those with a family history of FBC 62% knew of the possibility of MBC.

Delay in presentation (>3 months) occurred in two thirds of cases with a median delay of 7.5 months. This was a particular problem in black men (100%), government hospital cases (89%) and those aged >65 (86%). Participants were asked to respond to three statements:

- I feel less masculine as a result of having breast cancer (72% disagreed)
- Breast cancer has affected my sexual relationships (83% disagreed)
- I am embarrassed to remove my shirt in public (83% disagreed)

Table 7.2 Breakdown of cases with impaired masculinity [17]

Study group	Not affected	Affected
All	10 (56%)	8 (44%)
Black race	2 (29%)	5 (71%)
Government patient	3 (33%)	6 (67%)
Age >65 at diagnosis	3 (43%)	4 (57%)
MBC aware	5 (83%)	1 (17%)
Delayed presentation	6 (50%)	6 (50%)
In a relationship	10 (62%)	6 (38%)

These apparently optimistic results faded somewhat when subgroup analysis was performed as shown in Table 7.2.

Taken together these results suggest that there is a largely unfilled need for better communication and support for men with breast cancer. This is unlikely to be forthcoming until national and international collaborations focus on techniques for reaching and adequately communicating with men with this rare disease.

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Chapter 8
Surgery

Abstract Most males with breast cancer have been treated by mastectomy irrespective of the psychological impact of changed body image. Nowadays selected cases can be treated by breast conserving surgery (BCS), that is, nipple conserving surgery for MBC. In the absence of controlled randomised trials, large databases such as SEER have been analysed and results suggest similar cancer specific survival in males treated with lumpectomy and radiotherapy compared with mastectomy. In another study there was reduced morbidity after BCS in terms of lymphoedema or shoulder movement limitation but with no difference detected in disease-free and overall survival. Sentinel node biopsy using dye and/or isotope has been shown to achieve comparable identification rates in MBC compared with FBC and this will serve to reduce subsequent lymphoedema risk. Reconstruction using skin flaps can be useful to obtain skin closure after mastectomy for extensive chest wall disease. Transverse rectus abdominis (TRAM) flaps are useful because they not only replace the skin and fat but also provide hair-bearing cover similar to the male breast skin. Ductal carcinoma in situ (DCIS) comprises up to 10% of MBC usually presenting as a lump or nipple discharge. Nipple preserving surgery is a valid option for selected cases of male DCIS, provided that tumour-free margins can be achieved and this should be followed by breast irradiation.

I am in this earthly world where to do harm is often laudable – to do good sometimes accounted dangerous folly. William Shakespeare

Surgical management of MBC, like other treatment modalities, has been largely copied from results of large studies of FBC. Since the 1980s, FBC has whenever possible been treated with breast conserving therapy with a shift from axillary clearance for all cases of invasive disease to selective clearance after either pre-operative confirmation of cytological/histological involvement or following sentinel node positivity. For those individuals needing mastectomy because of extent of disease or recurrence after breast-conserving therapy, breast reconstruction is being considered for most cases. Treatment of MBC is taking a considerable time to catch up with the advances that have been made in women with breast cancer. Bedevilling the available results is the lack of randomised controlled trials because of the, until recently, minimal cooperation between groups in investigating this rare disease.

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Mastectomy and Breast Conserving Surgery

Mastectomy has been the standard offer to males with operable breast cancer with scant regard for the psychological impact of change in body image. There has been a gradual emergence of breast conserving, that is, nipple conserving surgery for MBC. In 1973, 257 Danish MBC cases diagnosed between 1943 and 1972 were reported, with the majority, 197 (78%) having operable disease [1]. Of these only 15 (8%) had local excision (Table 8.1). Radiotherapy was administered to 77% but was sole primary treatment in six cases. Between 1942 and 1871 there were 200 MBC treated at the Christie Hospital Manchester [2]. Of these 159 had local treatment 76 stage I, 38 stage II and 45 stage III. Radiotherapy alone was used in five patients with stage I disease because of comorbidity contraindicating general anaesthesia.

In a remarkable collaboration between 11 cancer centres taking part in the International Patient Data Exchange System a cohort of 335 MBC was assembled [3]. Of these 308 had operable disease and being slightly more recent there was a drift from radical surgery and breast conserving surgery was used in 30 (10%). Goss reported 229 Canadian cases, of whom 168 were treated by radical or simple mastectomy and 20 had a local excision combined with axillary clearance in 8 (3.5% of total) [4].

Golshan et al. reported seven cases of MBC in whom lumpectomy alone was used to extirpate the primary tumour [6]. Average age at diagnosis was 61 years (range 38–86). The mean tumour size was 1.7 cm (T1 5, T2 1, Tis 1). Of the six invasive cancers all were ER+ve and interestingly, two (33%) proved to be HER2+ve. All received adjuvant tamoxifen and radiotherapy with three receiving adjuvant chemotherapy. After a median follow-up of 67 months there had been no recurrences.

Lanitis et al. described a 50 year-old male with a 1 cm cancer at 6 o'clock to the left nipple who refused any operation to remove the nipple [7]. He was treated by wide excision, sentinel node biopsy and axillary clearance. Histology showed a 7 mm grade II ductal cancer with associated intermediate grade DCIS, completely excised, with 1/9 axillary nodes involved. He received 4 cycles of adjuvant chemotherapy (adriamycin and cyclophosphamide) followed by chest wall irradiation then tamoxifen for 5 years subsequently switching to letrozole. There had been no evidence of recurrence 8 years after surgery. Subsequently Niikura et al. reported a

Table 8.1 Local treatment in large series of MBC

Author	N	RM	SM	LE	Radiotherapy
Scheike 1974 [1]	257	57	100	15	141 (77%)
Ribeiro 1977 [2]	200	77	50	RT alone 32	
Guinee 1993 [3]	308	220	58	30	245 (80%)
Goss 1999 [4]	229			20	126 (55%)
Cutuli 2010 [5]	489	447		42	417 (85%)

case of non-invasive intracystic carcinoma in a 70 year old man, treated by excision, negative sentinel node biopsy and post-operative radiotherapy [8]. This achieved a very good cosmetic result with no reported recurrence.

The largest series consisted of 489 French cases diagnosed between 1990 and 2005 but even with this relatively recent cohort only 42 (8.6%) had breast conserving surgery [5]. Nevertheless the importance of the axillary nodal status was becoming better appreciated and axillary surgery was performed in 469 (96%). The procedure was a clearance in 436 (90%), sentinel node biopsy in 33 (7%) with completion axillary clearance in 24 (5%).

There were 22 new MBC cases treated at Stanford University Medical Center between 1960 and 2011 and 14 (64%) were treated by radical or modified radical mastectomy, 4 (18%) by simple mastectomy and 4 (18%) with breast conserving surgery [9]. Some form of axillary surgery was performed for 21 (95%).

Cloyd et al. analysed the Surveillance, Epidemiology and End Results (SEER) of MBC patients treated between 1983 and 2009 [10]. Of 5425 males 4707 (87%) were treated by mastectomy and 718 (13%) underwent lumpectomy. Lumpectomy became used more frequently with time: 11% between 1983–1986 increasing to 15% in 2007–2009. No lymph node sampling was performed in 34% and only 35% had adjuvant radiotherapy after lumpectomy. Ten-year breast cancer-specific survival was 83% in lumpectomy patients and 77% in those treated by mastectomy patients. There was no independent association of lumpectomy with worse breast cancer-specific survival.

In a partially overlapping study, 2013 Fields et al. reported a stage specific analysis of surgical management of MBC in the USA, using the SEER database of 4276 cases diagnosed between 1973 and 2008 [11]. Most cases were treated by mastectomy with breast conserving surgery being used in only10%. For those with localised disease, there was similar cancer specific survival in males treated with lumpectomy and radiotherapy compared with mastectomy (hazard ratio 1.33; 95% CI 0.49–3.61; P = 0.57).

Fogh et al. reported a series of 42 MBC cases treated at Massachusetts General Hospital or Boston Medical Center between 1990 and 2003 [12]. Surgery comprised modified radical mastectomy (MRM) in 30, simple mastectomy (SM) in 4 and breast conserving surgery (BCS) in 8 (19%). Musculoskeletal function including tissue fibrosis, arm oedema, and range of shoulder movement were assessed by a multidisciplinary group. Results are summarized in Table 8.2 which shows the reduced morbidity after BCS with no lymphoedema or limitation of shoulder movement. There was no difference detected between the three procedures in terms of disease-free and overall survival.

Table 8.2 Morbidity after surgery for MBC [12]

Procedure	Fibrosis	Lymphoedema	Shoulder restriction
MRM (n = 30)	4 (13%)	7 (23%)	8 (27%)
TM (n = 4)	2 (25%)	0	2 (50%)
BCS (n = 8)	1 (13%)	0	0

Table 8.3 5 year cause specific survival in relation to local treatment method (Zaenger 2015) [13]

	Stage I disease		Stage II disease	
Local treatment	N	5 year survival	N	% 5 year survival
MRM	490	97%	275	91%
MRM + RT	33	100%	42	94%
SM	399	97%	198	91%
SM + RT	23	100%	21	73%
BCS	117	96%	44	92%
BCS + RT	103	100%	32	100%

Zaenger et al. conducted another analysis of the SEER database focusing on the 1777 males with stage I/II, T1/2, node negative disease, treated between 1998 and 2011 [13]. The majority were treated by radical or simple mastectomy, with or without post-operative radiotherapy. As is shown in Table 8.3, only 296 (17%) were treated by breast conserving surgery with post-operative radiotherapy being given to 135 (46%). Early results showed no deaths in those treated by mastectomy or BCS when post-operative radiotherapy was given. There was no difference in survival and no deaths in those with stage I or stage II disease who were treated by BCS and radiotherapy. This needs to be interpreted with caution because of the relatively short duration of follow-up.

MRM alone had an actuarial 5-year CSS of 97.3% for stage I and 91.2% for stage II patients. No deaths were recorded in the BCT group, regardless of stage, or in the three stage I surgical groups if the men received RT, with an actuarial 5-year CSS of 100% in each BCT group.

Sentinel Node Biopsy

Over a 3 year period ending November 2009, 16 MBC cases underwent sentinel node biopsy (SNB) at the Memorial Sloan-Kettering Cancer Center (MSKCC), using both dye (isosulfan blue) and radioisotope (Tc-99m unfiltered sulphur colloid) [14]. The sentinel node was correctly identified in 15 (94%) being hot and blue in 14, and blue only in 1 case. There was nodal positivity in 5 (33%), (2 on frozen section and 3 on deeper sectioning or immunohistochemistry). Results of this and other series are shown in Table 8.4 [14–22]. The MSKCC experience was updated by Flynn et al. when a 97% identification rate was achieved in 77 SNB procedures [21].

The University of Michigan Comprehensive Cancer Center reported 6 SNBs performed for MBC with a 100% identification rate. In a first report from the MD Anderson Cancer Center of 7 cases SNB was identified in every one [16] and this was maintained in a follow-up report of 30 SNBs [18]. The European Institute of Oncology also reported 100% identification rates in 2004 [17] and 2006 [20]. In a Hungarian study conducted at Bács-Kiskun County Teaching

Table 8.4 Results of sentinel node biopsy in MBC

Author	N	Technique	Identification	Node positive
Port 2001 [14]	16	IB & Tc	94%	33%
Cimmino 2002 [15]	6	IB & Tc	100%	50%
Albo 2003 [16]	7	IB & Tc	100%	14%
De Cicco 2004 [17]	18	Tc	100%	33%
Boughey 2006 [18]	30	IB & Tc	100%	37%
Rusby 2006 [19]	31	IB/Tc 16 IB 5 Tc 10	90%	55%
Gentilini 2007 [20]	32	Tc	100%	19%
Flynn 2008 [21]	78	IB & Tc	97%	49%
Maraz 2014 [22]	25	IB & Tc	100%	48%

IB Isosulfan blue, *Tc* Technetium-99m

Hospital SNB was performed with both dye and isotope successfully in all 16 cases [22]. After a median follow-up of 48 months, there had been no axillary recurrence after SNB.

Reconstructive Surgery

Reconstruction using skin flaps has usually been performed in order to achieve skin closure after mastectomy for MBC. In 1984 Chastel et al. described two males who underwent a modified radical mastectomy [23]. Because of the extent of the defect, a triple L-shaped transposition (Limberg) flap was used to achieve a satisfactory result. Spear and Bowen carried out a transverse rectus abdominis (TRAM) flap, arguing that it may be the best choice for reconstruction after mastectomy for MBC because not only does it can replace the skin and fat but also because it provides hair-bearing cover similar to the native male breast skin [24]. Others have also reported successful use of the TRAM flap in the reconstruction of the tissue deficit after mastectomy [25, 26].

Nakao et al. reported an unusual case of advanced MBC in a patient with chronic renal failure who was on haemodialysis [27]. He had multiple pulmonary metastases and was treated with neoadjuvant fluorouracil and epirubicin (280 mg), after which the pulmonary metastases disappeared. He then went on to have a radical mastectomy and reconstruction for the chest wall defect using a delto-pectoral flap (DP) flap. The patient remained well without apparent local recurrence or distant metastasis after 2 years. The authors concluded that this was a valid approach for a very debilitated patient.

Yamamura described a 61-year-old male patient presented with an 85 mm × 51 mm hard mass in the left axilla [28]. This proved to be an adenocarcinoma arising within an accessory mammary gland. Staging showed no distant spread so he received 6 cycles of neoadjuvant FEC which reduced the tumor size to 55 mm. Subsequently he underwent complete resection with clear surgical margins and the

Table 8.5 Incidence of DCIS in larger series of MBC

Author	N	DCIS	Age
Treves 1955 [29]	146	7 (4.8%)	
Holleb 1968 [30]	198	12 (6.1%)	
Norris 1969 [31]	113	8 (7.1%)	
Schieke 197 [31]	176	5 (2.8%)	
Borgen 1992 [32]	104	16 (15.3%)	
Salvadori 1994 [33]	170	4 (2.4%)	
Stierer 1995 [34]	169	8 (4.7%)	
Cutuli 1997 [35]	621	31 (5%)	58
Donegan 1998 [36]	217	12 (9.4%)	
Goss 1999 [4]	229	4 (1.7%)	
Anderson 2005 [37]	2984	280 (9.4%)	62
Harlan 2010 [38]	512	58 (11.3%)	60

resulting skin defect was closed using a latissimus dorsi (LD) flap. He remained disease-free during the 4 years after the operation.

Ductal Carcinoma in Situ

Ductal carcinoma in situ is a rare histological subtype of a rare disease so information is relatively limited. In the larger series of MBC cases (>100 patients) the incidence of DCIS varied from 1.7% to 15.3% with a mean of 12.2% as shown in Table 8.5 [1, 4, 29–38]. In three separate series of male DCIS cases the median ages at diagnosis were 58 [35], 62 [37] and 60 [38] years. This contrasts with median age at diagnosis of MBC reported as being approximately 65 years in unselected larger series.

Anderson and Devesa compared MBC and FBC using a SEER database of cases diagnosed between 1973 and 2001 and reported that DCIS comprised 280/2984 (9.4%) of male cases and 53,928/454,405 (11.9%) of FBC [37]. Probably as a result of better investigation DCIS rate increased 1.2-fold in males and because of mammographic screening it increased 5.5-fold in women during this time.

Presenting Symptoms

Hittmair et al. reviewed the Armed Forces Institute of Pathology specimen archive and found 84 cases of pure DCIS [39]. Median age at presentation was 65 years, with 2 months median duration of symptoms. The commonest symptom was a lump, present in 49 (58%), followed by bloody nipple discharge in 29 (35%). Unilateral gynaecomastia affected 15 (18%) with one case complaining of bilateral

Table 8.6 Histological subtypes of male DCIS

Subtype	Cutuli 1997	Hittmair 1998	Anderson 2005
Papillary	7	39	49
Papillary + cribriform	5	23	
Cribriform	3	16	
Apocrine	1		
Comedo	3		12
Solid		5	
Micropapillary		1	
DCIS NOS	12		39

gynaecomastia and another with mastitis. In the large French series of MBC there were 31 DCIS cases comprising 5% of the total [36]. The presenting symptom was either a lump in 19 (61%) or bloody nipple discharge in 12 (39%).

Histology

There have been three comprehensive studies analysing the histological subtypes in male DCIS and these are summarised in Table 8.6 [36, 38, 40]. Allowing for differences in nomenclature, the papillary subtype emerges as the commonest variant, followed by mixed papillary and cribriform. Hittmair et al. reported that 74% of cases were papillary often combined with a cribriform pattern [40]. Frequently there was extension of DCIS beyond the main papillary tumour. Among the pure DCIS cases none had high grade disease, 48 (57%) were low and 36 (43%) were of intermediate grade.

Surgery

Surgery has varied between the extremes of radical mastectomy and lumpectomy alone, and even in the absence of data from randomised controlled trials certain conclusions can be drawn from the disparate reports. In 1979, Cole and Qizilbash reported 2 cases of ductal carcinoma in situ (DCIS) of the male breast [40]. The first was a 64-year-old man with a bloodstained right nipple discharge and a 1 cm painless mass medial to the nipple present for 6 months. The lump was excised and proved to be DCIS without invasion. Four years later he was seen with a lump at the same site and this was biopsied and shown to be invasive cancer. He developed further recurrences including bone metastases before being lost to follow-up. The second case was a 32-year-old man with a right breast lump present for 6 months. He had no discharge or pain and was in good health with no medication. The subareolar mass mobile measured 3 x 2 cm. It was excised leaving the nipple in place.

Histology showed gynaecomastia with superimposed DCIS. One year later there was no evidence of recurrence. The authors were prompted to review 233 cases of gynaecomastia but found no evidence of malignancy in any of the specimens.

In the series of 113 cases reviewed by Norris and Taylor at the Armed Services Institute of Pathology (AFIP), there were 8 with DCIS and 9 with papillary carcinoma [32]. Among the latter group there were 2 deaths from metastatic disease but none in the eight with DCIS. Noguchi et al. treated an 80 year-old man with a 3 cm smooth soft mass in the left breast shown by ultrasound to be cystic, Cyst fluid contained no malignant cells but when the cyst wall was excised a rice grain sized mass was found which was a non-infiltrating medullary tubular carcinoma. Subsequent simple mastectomy showed no residual cancer.

At the Lahey Clinic, between 1968 and 1991, 23 MBC cases were treated and of these 4 (17%) had DCIS without invasion [41]. Of these 3 had a retro-areolar lump and one presented with a bloody nipple discharge. Three of the lesions were intracystic papillary and the other was papillary. Surgery was partial mastectomy in 2 and both recurred after 30 and 108 months so that salvage mastectomy was necessary. In the 3 who had axillary dissection there was no evidence of nodal spread. All patients were alive without disease after a median follow-up of 78 months. After a median follow-up of 83 months, 4 developed local relapse and 3 had had lumpectomies. Of the relapses 3 were invasive and one was DCIS. One of these patients died of metastatic disease 30 months later.

In Harlan's series of 58 male DCIS cases 38 (66%) were treated by mastectomy, one also received postoperative radiation [39]. Breast conserving surgery was performed in 18 cases with 7 receiving breast irradiation. Two cases had no surgical intervention. No axillary surgery was carried out in 41 (70%), 8 (14%) had axillary dissection and 9 (16%) had sentinel node biopsy leading on to axillary dissection in 2 cases. Adjuvant tamoxifen was given to 6 cases (10%). Unfortunately no data was available covering relapse-free survival of these cases.

Recommendations

Nipple preserving surgery is a valid option for selected cases of male DCIS, provided that tumour-free margins can be achieved. This should be followed by breast irradiation, based on RCTs in females which showed a benefit from radiotherapy in all types of DCIS, irrespective of DCIS grade or extent. The EORTC 10853 trial identified that the risk factors for recurrence were patient age, margin involvement and not receiving radiotherapy [42]. In multivariate analysis margin status was a more significant predictor of risk of recurrence than withholding breast irradiation. Pure DCIS will not metastasise but because small foci of invasion can be missed it is sensible to carry out a sentinel node biopsy at the time of wide excision or mastectomy. Adjuvant tamoxifen in patients with ER+ve tumours may reduce the risk of recurrence and progression to invasive disease and additionally will diminish the likelihood of contralateral disease.

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Chapter 9
Adjuvant Therapy

Abstract No randomised controlled trials of adjuvant therapy have been conducted with MBC patients so that the results from large trials in FBC have been applied to MBC with varying degrees of success. Because the tumours are predominantly ER+ve adjuvant endocrine treatment has been most widely prescribed. The reported studies used a variety of controls, historic or untreated, but not necessarily similar in all aspects apart from therapy. All appeared to show a benefit for tamoxifen-treated cases. Males commonly suffer side effects from tamoxifen including reduced libido, weight gain, hot flushes and altered mood which lead to cessation of treatment in up to 35% of cases. After adjustment for age, tumour size, grade and axillary nodal status there is a 1.5 fold increase in mortality in men given aromatase inhibitors rather than tamoxifen. Adjuvant chemotherapy has been given to a complex mixture of cases using a variety of regimens and no differences in overall survival emerged for those given chemotherapy compared with those who were not. Post-mastectomy radiotherapy may reduce the incidence of local relapse but has not been shown to significantly improve prognosis, possibly because of non-randomised and underpowered studies.

> *The statistical method is required in the interpretation of figures which are at the mercy of numerous influences, and its object is to determine whether individual influences can be isolated and their effects measured. The essence of the method lies in the determination that we are really comparing like with like, and that we have not overlooked a relevant factor which is present in Group A and absent from Group B. The variability of human beings in their illnesses and in their reactions to them is a fundamental reason for the planned clinical trial and not against it*. Austin Bradford Hill

Adjuvant Endocrine Therapy

The preponderance of estrogen receptor positive (ER+ve) MBC has meant that since the notion of adjuvant therapy became evidence-based there has been a predominance of endocrine based treatment. This has occurred in a randomised trial-free environment. In 1978, Ribeiro and Swindell pioneered treatment for MBC with

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Table 9.1 Results of adjuvant endocrine therapy

Author	Treated	Survival	Comment
Ribeiro 1992 [1]	Tamoxifen 30	5 year DFS 56% v 25%	Historic controls
Giordano 2005 [2]	Tamoxifen 36	10 year OS 65% v 45%	Untreated historic controls
Cutuli 2010 [3]	Tamoxifen	Metastasis-free S 62% v 24%	Node positive cases
Fogh 2011 [4]	Tamoxifen	10 year OS 100% v 65%	Tam + RT versus Tam
Hong 2016 [5]	Tamoxifen	Median survival 8.5 v 4.2 years	Untreated controls

a non-randomised trial for cases with axillary nodal involvement [1]. They investigated the role of tamoxifen which was originally given at a dosage of 20 mg daily for 1 year. After 1988, when the Oxford Overview of tamoxifen trials for FBC showed an increased benefit for 2 years of treatment, the duration of tamoxifen was extended accordingly. Of the 39 treated cases, side effects were responsible for 2 stopping (alopecia and skin rash) and 7 had a change of treatment after relapse but the remaining 30 cases completed the course of tamoxifen. Historical stage-matched controls were used for comparative purposes and as is shown in Table 9.1 there was a significant improvement in disease-free survival (DFS), 56% versus 25%.

Between 1955 and 1997, 229 MBC cases were treated at Princess Margaret Hospital Toronto and of these 215 had surgery which was predominantly mastectomy (96.5%) with only 8 cases having a lumpectomy [6]. Treatment comprised surgery (49) surgery and radiotherapy (98), surgery and endocrine therapy (29), surgery and chemotherapy (13), surgery radiotherapy and endocrine therapy (23). Multivariate analysis indicated that receiving adjuvant chemotherapy was associated with a significant improvement in both disease-free and overall survival.

Takei et al. described a 40-year-old man with a grade II, stage I MBC who was treated by mastectomy followed by 2 years of tamoxifen and fluorouracil [7]. Shortly after completing the course he developed an ER+ve recurrence. Despite hormone therapy and chemotherapy, proliferation of the metastatic disease continued with the patient dying 2½ years later. During this period, serum estradiol rose from 18.0 pg/ml to 892.3 pg/ml. The authors' opinion was that there high aromatase activity within the metastatic disease so that adjuvant tamoxifen treatment should be extended to 5 years or longer to reduce the risk of early recurrence of ER+ve disease.

Discouraging results were reported from the US Veterans Administration nationwide cancer registry [8]. Tumour specimens from 65 MBC cases of male breast cancer were reviewed centrally both for histopathology and immuno-histochemical characterisation of receptor status. Although those patients with ER+ve tumours had a better survival than ER-negative cases on univariate analysis, this lost significance on multivariate analysis. Furthermore benefit from tamoxifen disappeared on multivariate analysis and the same was true for PR+ve cases.

Giordano et al. reviewed 156 MBC cases treated at the MD Anderson Cancer Center between 1944 and 2001 [2]. Of these 135 had non-metastatic disease, 74 (55%) were node positive and of the tumours, 115 (85%) were ER+ve with 96 (71%) being PR+ve. Adjuvant hormonal therapy was given to 38 with 36 (92%) receiving tamoxifen, 1 having an orchidectomy and megestrol and 1 receiving a GnRH analogue (8%). Of those given adjuvant hormonal therapy, 31 (82%) had ER+ve cancers, 6 (2%) were ER unknown and 1 was ER–ve. When overall survival of those treated with endocrine therapy (39) was compared with that of 97 who received no adjuvant endocrine treatment there was a significant improvement at 10 years, 65% versus 45% (hazards ratio 0.45, p = 0.01).

Ngoo et al. reported 6 MBC cases treated at the Malaysia Medical Centre between 2003 and 2007 [9]. In terms of ethnic origin, 4 were Chinese origin and 2 were Malay. Surgery was mastectomy and axillary clearance (4), simple mastectomy (1) and wide excision (1). Two patients were given adjuvant chemotherapy and chest wall irradiation. All received adjuvant tamoxifen and after a median follow-up of 37.5 months, none had relapsed.

In the large French series of 489 MBC cases, 352 (72%) received adjuvant endocrine treatment [3]. This comprised tamoxifen alone for 298 (85%), aromatase inhibitors alone (35) and tamoxifen followed by AI (9) and other combinations. Among the 223 node negative patients the rate of metastatic disease was reduced from 15% to 10% by endocrine therapy but this difference did not achieve statistical significance. There were 243 men with pathologically involved axillary nodes and within this group endocrine therapy reduced the rate of metastases from 62% to 28%. There were similar event rates in those treated with tamoxifen or aromatase inhibitors, metastases 21% versus 28% and deaths 22% versus 24%.

Fogh et al. reviewed 42 MBC cases treated between 1990 and 2003, all of whom had ER and PR+ve tumours [4]. Adjuvant tamoxifen was given to 21 (50%), chemotherapy to 18 (43%), and post-operative radiotherapy to 11 (26%) and the median follow-up was 8 years. The 10-year overall survival in those treated by tamoxifen and radiation was 100%, compared with 65% in those who received tamoxifen alone, 83% with radiation alone ($P = .05$), and 65% without adjuvant therapy. In this univariate analysis, adjuvant chemotherapy alone or combined with tamoxifen or radiation had no significant impact on 10-year overall survival.

Contrasting results were reported by Liu et al. in a cohort of 87 Chinese MBC patients, treated by radical (40) or modified radical mastectomy (47) [10]. Of the 58 patients with known receptor status 50 (86%) were ER+ve and 44 (76%) were PR+ve. After surgery, 56 (64%) received adjuvant chemotherapy (18 CMF, 17 CAF, 15 TA, and 6paclitaxel/anthracycline/cyclophosphamide (TAC)). Radiotherapy was administered to 37 (43%) and endocrine therapy to 45 (52%), as tamoxifen (42) and letrozole (4). Multivariate analysis of factors significantly affecting 5 year overall survival showed that tumour size, stage nodal status and use of adjuvant chemotherapy were significant, In contrast, age, radiotherapy, and hormonal therapy had no significant impact on the 5-year OS.

Similar findings were reported in a series of 25 MBC cases treated at Sun Yat-Sen University Cancer Center between 2000 and 2011 [11]. Of these, 20 were treated by

mastectomy and 1 by lumpectomy. Receptors were measured in 19 and 16 (84%) were ER/PR+ve. Adjuvant chemotherapy was given to 16, 3 as neoadjuvant but endocrine therapy was administered to only 7 (28%), either as tamoxifen or toremifine. Radiotherapy to the chest wall and gland fields was used in 1 case. Median follow-up was 51 months and the 5-year OS was 67%. Although adjuvant endocrine therapy was associated with better overall survival, this did not achieve statistical significance probably because of the small number of treated cases in these male breast cancer patients. In terms of survival, neoadjuvant chemotherapy, tumor size, lymph node status, distant metastasis and TNM stage were significant prognostic variables.

This contrasted with previous results from the same cancer centre. Zhou et al. studied 72 MBC patients treated between 1969 and 2009 [12]. The 5-year overall survival rate was 72%. Multivariate analysis revealed that significant factors for overall survival were tumour stage, (P = 0.035), disease operability (P = 0.021) and endocrine therapy (P = 0.019).

Recently Hong et al. reported a series of 50 Korean patients with operable MBC who had been treated at seven different centres [5]. Hormone receptor data were available for 42 patients and 38 (91%) were ER+ve and 27 (64%) were PR+ve. Use of adjuvant endocrine therapy improved overall survival in patients with ER+ve tumours (median survival 8.5 years versus 4.2 years) for those not given endocrine treatment.

Compliance

Annelli et al. investigated the side effects of adjuvant tamoxifen treatment in 24 MBC cases seen between 1990 and 1993 [13]. Of these, 19 had ER−ve primary tumours and 15 (63%) complained of one or more side effects. The most frequent was reduced libido, which was a problem for 7 (29%). Six patients (25%) had weight gain, 5 (21%) had hot flushes and 5 (21%) suffered altered mood leading to depression in 4. Other side effects included insomnia (3) and deep vein thrombosis in one patient. As a result, 5 (21%) stopped taking tamoxifen within a year of diagnosis. The reasons given were decreased libido (2), hot flushes (2), and deep vein thrombosis (1). The authors concluded that whereas FBC cases had a discontinuation rate of 10% [14], males with the disease had a 21% dropout rate from side effects.

Endocrine therapy was used in 51 MBC cases treated at The Ottawa Hospital Cancer Centre between 1981 and 2003 [15]. Adjuvant treatment comprised tamoxifen (31), or anastrozole (3). Of those given tamoxifen as adjuvant or palliative treatment, 50% reported side-effects, the most frequent being hot flushes, followed by diminished libido, weight gain and malaise. Because of toxicity, 24% discontinued tamoxifen, in one case because of a pulmonary embolism. Despite anastrozole causing decreased libido, leg swelling and depression no patients stopped treatment.

Xu et al. examined tamoxifen adherence and its impact on mortality in a cohort of 116 MBC patients with ER+ve disease [16]. Of those scheduled to take 5 years of tamoxifen, after 1 year only 75 (65%) were actually doing so. The compliance

fell to 46% after 2 years, 29% at 3 years, 26% at 4 years, and only 18% % in the final year. The significant factors that reduced compliance were low social support, age and adverse side-effects. The10-year DFS of the compliant patients was 96% compared with 42% in the non-compliant group. Ten-year overall survival rates were 80% and 50% respectively, indicating the serious consequences of non-adherence.

Pemmaraju et al. reviewed 126 MBC patients seen at the MD Anderson Cancer Center between 1999 and 2009 [17]. Of these, 64 (51%) had operable disease and received tamoxifen. After a median follow-up of 3.9 years, 34 (53%) had reported side-effects of which the commonest were weight gain in 14 and sexual dysfunction in 14 patients. Toxicity led to discontinuation om 13 (20%), the reasons being ocular (1), leg cramps (1), neurocognitive problems (2), bone pain (2), sexual dysfunction (3), and thromboembolism in 4 cases.

Aromatase Inhibitors (AIs)

Adipose tissue is a major site of steroid biosynthesis, wherein P450 aromatase is expressed. Dieudonne et al. investigated at a cellular level whether sex steroids and leptin could regulate aromatase in cultured pre-adipocytes from male and female abdominal fat [18]. They reported that human recombinant leptin down-regulated P450 aromatase activity in female adipocytes. In contrast, leptin up-regulated (1.6-fold) P450 aromatase mRNA expression in male pre-adipocytes. Furthermore, in females, 17-β estradiol, decreased P450 aromatase by 50% whereas in males it up-regulated P450 aromatase mRNA expression (2.4-fold). In men, androgens increased 2.5–5-fold mRNA expression. It was suggested that the sex-specific differences might partially explain the sexual dimorphism of body fat distribution in humans.

In a similar study, adipocytes were cultured in suspension cultures and aromatase activity was measured with [1β-3^{H}]-androstenedione as substrate [19]. Addition of cortisol increased basal aromatase activity increased 3.5-fold in females but in males activity was inhibited by approximately 40%. Insulin did not independently alter aromatase expression, but the combination of cortisol and insulin abolished both gender-specific differences.

After the ATAC trial had shown the superiority of anastrozole over tamoxifen for adjuvant treatment of FBC it was assumed that this could be successfully applied to MBC [20]. Relatively small studies appeared to show a benefit from adjuvant anastrozole and letrozole but numbers were such that firm conclusions could not be drawn regarding adjuvant efficacy [2, 15]. To investigate with larger numbers of cases whether this was true, Harlan et al. analysed outcomes in 512 MBC cases derived from the Surveillance, Epidemiology and End-Results (SEER) database [21]. Of these, 440 (86%) underwent mastectomy and 124 (28%) were given hormonal therapy (tamoxifen 95, AI 19, tamoxifen + AI 8, other 2). There was a significant reduction in cancer mortality among those given tamoxifen (HR 0.04) compared with those who had no systemic therapy. Most strikingly however adjuvant AIs did not reduce deaths (HR 1.2, 95% CI 0.4, 3.8).

Table 9.2 Comparison of efficacy of adjuvant endocrine therapy for MBC [22]

Adjuvant agent	N	Mortality
Tamoxifen	207 (81%)	47 (18%)
Aromatase inhibitor	50 (19%)	16 (32%)

Eggemann et al. studied 257 MBC patients with ER+ve disease reported to German cancer registries [22]. Of these 207 (81%) received tamoxifen and 50 (19%) received aromatase inhibitors (AIs). After a median follow-up of 42.2 months, among the tamoxifen treated group there had been 47 (18%) deaths compared with 16 (32%) in the AI group (Table 9.2). After adjustment for age, tumour size, grade and axillary nodal status there was a 1.5 fold increase in mortality on those given AIs.

These seemingly paradoxical results are probably due to the testicular production of estrogen which is not abolished by AIs [23]. In males, approximately 20% of estrogen is derived from the testes. For this reason, if tolerated, tamoxifen is the adjuvant endocrine therapy of choice in MBC. If AIs are being given in an adjuvant role their use should be combined with a GnRH analogue to abolish the hypothalamic drive to the testes.

Adjuvant Chemotherapy

Based on encouraging results from randomised controlled trials of adjuvant chemotherapy for FBC, a study was started at the US National Cancer Institute in 1974 to investigate the efficacy of adjuvant chemotherapy in males [24]. This non-randomised study comprised 24 node positive cases of MBC who received cyclophosphamide, methotrexate, and 5-fluorouracil (CMF). Adjuvant therapy was instigated within 4 weeks of surgery and none received postoperative radiotherapy. After a median follow-up of 46 months the actuarial five-year survival rate was >80%.

At the MD Anderson Hospital 11 consecutive patients with MBC were treated with adjuvant chemotherapy [25]. The regimen was fluorouracil, adriamycin and cyclophosphamide (FAC) in ten patients and CMF in one. Of the cases 7 were Stage II and 4 were stage III. After a median follow-up of 52 months, four patients experienced a relapse and seven remained disease-free. The estimated 5 year survival was 85%.

Izquierdo et al. reported a series of 50 MBC treated in Barcelona between 1964 and 1990 [26]. Adjuvant therapy was introduced in 1979 and 11 received chemotherapy, (CMF 4, FAC 1, CMF + tamoxifen 5, FAC + tamoxifen). After a median follow-up of 32 months the estimated 5 year survival for those given adjuvant chemotherapy was 80%. Donegan et al. studied 217 MBC cases derived from 18 tumour registries in eastern Wisconsin between 1953 and 1995 [27]. Of these, 30 received adjuvant therapy and 22 were given a combination of chemotherapy and endocrine therapy. When the subgroup who were node positive and ER+ve and

had chemotherapy ± endocrine therapy were analysed there was a significant difference in survival compared with untreated cases (0% versus 50% at 10 years).

The Breast Cancer Working Committee of the Autologous Blood and Marrow Transplant Registry reported outcomes of high-dose adjuvant therapy in combination with autologous haematopoietic stem cell support (autotransplants) in 13 MBC cases treated in 10 centres [28]. There were 6 stage II cases, 4 stage III and 3 stage IV. This was a selected young population with a median age of 50. All tumours were ER+ve receptor positive. Five received cyclophosphamide, thiotepa and carboplatin and 8 were given other alkylator-based regimens. Three patients had bone marrow, eight were given blood stem cells and two received both. Of the ten who had received autotransplants, three relapsed and died. Seven of 10 (70%) were disease-free after a median follow-up of 23 months.

A series of 121 MBC patients were treated at Ankara Oncology Hospital between 1972 and 1994 [29]. Of these 72 (60%) had systemic adjuvant treatment. Receiving adjuvant chemotherapy was significantly associated with improved survival (no chemotherapy versus chemotherapy, RR = 1.4, 95% CI 1.3, 3.9).

Vinod and Pendlebury reviewed the results of adjuvant therapy for MBC at the Royal Prince Alfred Hospital [30]. Between 1983 and 1996, 24 men were referred for treatment of breast cancer and of these, 19 had localised disease, 12 T1, 5 T2 and 2 T4 cancers. Eleven (58%) patients had nodal involvement. Median age was 57.5 years and follow-up was 6.2 years. Receptor status was ER+ve 10, ER−ve 2 and unknown 7. All had a mastectomy and 11 (58%) received radiotherapy. Ten received adjuvant systemic therapy, 4 had chemotherapy alone, 3 received chemotherapy and tamoxifen, and three patients were given tamoxifen only. Seven patients relapsed (one local, five distant, one both). Of those with distant relapse, 4/6 had no systemic therapy. Both node-positive patients given no systemic treatment relapsed. Local control rates were 88% (7/8) in patients who had mastectomy alone and 91% (10/11) in those patients receiving adjuvant radiotherapy.

Wang-Rodriguez et al. reported outcome for a series MBC patients derived from the US Veterans Administration cancer registry [8]. Of these, 15 had received adjuvant chemotherapy but unfortunately the indications were not consistent and the regimens not standardised. There was no detectable difference in survival between those given adjuvant chemotherapy compared with the 47 MBC cases treated by surgery alone.

The MD Anderson experience with adjuvant therapy for MBC was updated in 2005 [2]. By this time, 32 men had been treated with adjuvant chemotherapy, 19 of them also receiving endocrine therapy. Various regimens were used, 23 had anthracycline-based regimens: fluorouracil, adriamycin, cyclophosphamide (FAC), fluorouracil, adriamycin, cyclophosphamide, methotrexate, vinblastine (FAC-MV), vincristine, adriamycin, cyclophosphamide, prednisone (VACP), cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) and adriamycin, cyclophosphamide (AC). Five received CMF and 3 had additional taxane. For those with node positive disease who received chemotherapy there were lower hazards for both recurrence-free and overall survival but this was not statistically significant.

Walshe reported 20 year survival data for 31 MBC cases treated with adjuvant CMF in study MB-82 at the National Cancer Institute between 1974 and 1988 [31].

Median patient age was 61 years and all were node positive, 21 (68%) with 1–3 involved nodes and 10 (32%) with ≥4 nodes. Treatment was given for 12 cycles. Ten patients remained alive at a median of 19.2 years. The actuarial survivals at 10, 15 and 20 years were 65%, 52% and 42% respectively and it was concluded that adjuvant chemotherapy may benefit node positive MBC patients.

In the French series of MBC cases, adjuvant chemotherapy was given to 164/489 (34%) [3]. There was an inverse relation with age: chemotherapy was used in 61% of those <50, 42% in the 50–70 age group and only 13% of those aged >70 years. Chemotherapy combinations varied but 120 (73%) received an anthracycline based regimen (FAC 18, FEC 102). No relapse-free or survival data were available in relation to adjuvant chemotherapy.

Liu et al. reported 5 year disease-free survival for 87 MBC cases treated at Tianjin Medical University Cancer Institute between 1961 and 2008 [10]. Of these 39 (45%) were aged ≥60 and 39 (45%) were node positive. Adjuvant chemotherapy was administered to 56 (64%) and was not standardised: CMF 18, CAF 17, TA (paclitaxel adriamycin) 15, TAC (paclitaxel adriamycin cyclophosphamide) 6. Paradoxically, the 5 year DFS for those given adjuvant chemotherapy was 54% whereas for those who received no chemotherapy it was 74%. The likely explanation was that chemotherapy was used in those with an inherently poorer prognosis.

Kiluk et al. studied 58 cases of MBC with operable disease and compared the adjuvant therapy received with that recommended by the US National Comprehensive Cancer Network [32]. There were 28 with stage I disease and of the 6 recommended for chemotherapy this was actually given to 4. For stage II (21 cases), the respective numbers were 14 and 12. There were 9 with stage III MBC and 6 (68%) received adjuvant chemotherapy. Results were not available in relation to adjuvant chemotherapy and disease-free survival. The Central Hospital of Tai'an reported 42 MBC cases with 24 receiving chemotherapy and their 5-year survival was 56% compared with 49% for those not given chemotherapy [10]. A recent publication from Korea illustrates the difficulty in disentangling the respective effects of adjuvant endocrine and chemotherapy [5]. Of a series of 59 MBC cases, 45 underwent curative surgery and of these, 19 had nodal involvement. Of the 42 with known ER status 38 (90.5%) were ER+ve. Adjuvant chemotherapy was given to 19 (42%), ACT 7, FAC 5, CMF 2, epirubicin, docetaxel (ET) 1, epirubicin carboplatin 1, adriamycin 1, paclitaxel 1 and fluorouracil 1. Endocrine treatment was used in 27/45 (77%) of those with known ER positivity. From this complex mixture of cases and systemic treatments no differences were detected in overall survival of those given chemotherapy compared with those who did not.

Radiotherapy

In the absence of randomised controlled trials the only evidence of efficacy of radiotherapy derives from comparative studies in which undisclosed selection may have biased the results. Robison and Montague reported a series of 39 previously

Table 9.3 Effect of adjuvant radiotherapy for MBC

Author	N	Follow-up (months)	5 year OS
Robison 1982 [32]	15	–	53%
Erlichman 1984 [33]	57		67%
Molls 1986 [34]	34	–	70%
Schuchardt 1996 [35]	17	53	42%
Ulutin 1988 [36]	15	227	60%
Stranzl 1999 [37]	31		77%
Chakravarthy 2002 [38]	13	96	75%
Zabel 2005 [38]	31	52	57%
Atahan 2006 [40]	42	29	77%
Cutuli 2010 [7]	356	58	81%
Yu 2011 [42]	46	46	60%

untreated MBC cases seen at the MD Anderson Hospital between 1948 and 1978 [33]. Of these 21 underwent mastectomy and 15 received post-operative radiotherapy to the chest wall and gland fields. Axillary nodal involvement was present in one case treated by radical mastectomy alone and in 8 of those who also were irradiated. Of the OS was 53% compared with 33% of the group that had surgery alone (Table 9.3).

In a report from the Princess Margaret Hospital Toronto, there were 89 MBC cases and 57 received post-surgical radiotherapy [34]. When the irradiated and non-irradiated cases were compared the 5 year OS were 50% and 67% respectively. This was probably was because the irradiated group had more extensive disease.

Molls et al. reported 34 men MBC cases who received 45Gy over 5 weeks with a 5-year survival rate of 70% [35]. They were unable to determine whether radiotherapy improved survival but concluded that treatment did reduce the risk of local relapse. Schuchardt et al. gave adjuvant radiotherapy to 17 MBC cases, all of whom were treated by radical mastectomy [36]. After a median follow-up of 53 months, 42% were alive without recurrence. Although better results were seen in node negative, younger patients and those with delay of < 3 months, this did not achieve statistical significance. Between 1980 and 1995, Ulutin et al. treated 15 MBC cases of which two were stage I, 9 stage II, and 4 stage III [37]. All patients had a mastectomy followed by external beam treatment 2Gy daily. Median follow-up was 227 months and the 5-year survival rate was 60%.

Stranzl et al. gave chest wall irradiation (mean dose of 50Gy) to 31 MBC patients of whom 16 also had treatment of gland fields [38]. Tumour stages were: stage 0 (2), stage I (8), stage II (10) and stage III (11). Endocrine therapy was given to 9 and chemotherapy to three patients. Only one patient developed local relapse and the 5-year OS was 77%. For node negative cases the 5-year OS was 91% compared with Chakravarthy and Kim reviewed 44 MBC cases treated between 1967 and 1995 [39]. All had a mastectomy and 13 were given postoperative radiation (45-64Gy to the axilla, supraclavicular fossa and internal mammary chain). Of the 31 treated by surgery alone 15 were stage I, 13 stage II and 3 stage III, whereas among

the 13 irradiated cases none were stage I, 6 were stage II and 7 stage III. The 5-year overall survival was 75%. Zabel et al. irradiated 31 MBC patients giving 60Gy to the chest wall and in some cases 46Gy to the axilla [40]. The 5-year overall survival was 57% but significantly worse in those who were lymph node positive. One patient developed local recurrence after 29 months.

Atahan et al. reviewed 42 Turkish MBC cases, all of whom had postoperative irradiation 50Gy in 2 Gy fractions to chest wall and in some cases to the gland fields (percentage not given) [41]. There was axillary nodal involvement in 26 (62%) and 11 received neoadjuvant and 36 adjuvant adriamycin-based chemotherapy. After a median follow-up of 29 months, loco-regional relapse occurred in 9 (21%), distant recurrence in 2(5%), with both sites of relapse in 1 (2.5%). The 5-year OS was 77% but univariate analysis of clinico-pathological factors, and mode of treatment showed no relationship with disease-free survival suggesting that although radiotherapy reduced local relapse of MBC it had no influence on survival.

In Cutuli's large series of 417 French MBC cases, radiotherapy was administered to 356 (85%) [3]. There was axillary nodal involvement in 220 (53%). The supraclavicular fossa (SCF) was irradiated in 249 (70%), internal mammary nodes in 263 (74%) and the axilla in 53 (15%). Interestingly of the cases receiving SCF treatment, 112 (45%) were pathologically node negative. Although the median delivered dose was 48 Gy, the treatment varied between participating centres. On multivariate analysis the only significant variables affecting distant metastasis were tumour grade and extent of axillary nodal involvement.

To determine the effectiveness of postmastectomy radiotherapy (PMRT) in MBC, Yu et al. compared outcomes in those treated at the London Regional Cancer Program in Ontario between 1977 and 2006 [42]. During this time PMRT was advised for patients with close or involved tumour margins, positive axillary nodes, or T3 tumours. The analysis was conducted on patients eligible for adjuvant PMRT. There were 46 MBC cases who received PMRT and 29 who did not and the comparative features of the two groups are shown in Table 9.4. There were fewer stage III cases in the non-irradiated cases although this was not statistically significant. There was a significant reduction in loco-regional relapses in the PMRT and this was seen particularly in the high-risk cases. Despite this local control benefit, there was an increased risk of distant metastases in those treated with PMRT. In the absence of randomised trials this work provided fairly compelling evidence of the value of PMRT in improving local control for MBC.

A major part of the problem of quantifying the effect of PMRT arose from the relatively small number of treated cases. This was overcome by Eggemann et al. who reported a population-based study of 664 MBC patients treated in former East Germany [43]. All had a radical mastectomy and PMRT was given to 348 (52%). None received systemic adjuvant therapy and follow-up was between 19 and 38 years (median 26.2 years. The overall survival was similar in those treated with and without PMRT but this masked important differences which emerged when cases were analysed by stage. The 20-year overall survival of stage I cases treated by surgery alone was 30% compared with 20% in those given PMRT. In

Table 9.4 Comparison of results of PMRT or no PMRT (Yu 2011) [42]

	PMRT (n = 46)	No PMRT (n = 29)
Stage		
I	6 (13%)	9 (31%)
II	24 (52%)	16 (55%)
III	16 (35%)	4 (14%)
Tumour grade		
?	16 (35%)	14 (48%)
I	8 (17%)	5 (17%)
II	13 (28%)	6 (21%)
III	9 (20%)	4 (14%)
Node status		
–ve	21 (46%)	16 (55%)
+ve	25 (54%)	13 (45%)
Margins		
?	8 (17%)	7 (24%)
≤2 mm	8 (17%)	3 (10%)
>2 mm	30 (66%)	19 (66%)
Loco-regional relapse		
All	2 (5%)	7 (24%)
Low risk	2 (5%)	2 (7%)
High risk	0	5 (17%)
Distant relapse		
All	17 (37%)	2 (7%)
Low risk	2 (4%)	1 (3.5%)
High risk	15 (33%)	1 (3.5%)

stage II cases there was no significant difference in 20-year survival whereas there was a significantly better survival in stage III cases treated with PMRT (20% versus 8%).

Because the non-irradiated cases were significantly older than those treated with PMRT, a subgroup analysis was made of those aged < 75 years. In this age group PMRT significantly improved OS rates in patients with stage III cancer disease). The 10-year OS rate was 12% without RT and 31% after PMRT ($p < 0.001$). Conversely, in stage I cases 10-years OS was 59% and 50% respectively. At 20 years OS were 43% and 26% ($p = 0.028$). The authors suggested that the increased death rate in those with stage I disease was the result of side-effects of RT on the heart, lungs and oesophagus because in the early years this involved megavoltage irradiation using Cobalt-60 γ-radiation) radiation. Studies using modern radiotherapy techniques were needed to assess the risk benefit ratio of PMRT.

Madden et al. analysed a SEER database of 1337 MBC cases diagnosed between 1983 and 2002 [44]. All had been treated with surgery, radical mastectomy 19 (1%), modified radical mastectomy 1062 (79%), total mastectomy 143 (11%) and wide excision 113 (9%). Post-surgical external beam radiotherapy was given to 329 (25%). After a median follow-up of 7.3 years the type of surgery had no significant

effect on cause-specific or overall survival. In contrast with the findings of Eggemann et al. with improved overall survival in stage I disease at 10 years (81% versus 63%, p = 0.03). Although there was a trend towards improved survival in stage II and III disease this did not achieve statistical significance ($P = 0.15$). Multivariate analysis showed that increasing age, higher stage and grade, together with no postoperative RT were significantly associated with worse OS. After controlling for known ER status (n = 978), RT was no longer significant with only age, stage, grade, and ER negativity predicting for worse OS.

Upadyhay et al. reviewed 96 MBC patients treated at the All India Institute for Medical Sciences between 2005 and 2015 [45]. At presentation 8 (8%) were stage I, 27 (28%) stage II, 39 (41%) stage III and 22 (23%) stage IV. There were 69 (72%) who underwent surgery which was either mastectomy or wide local excision and 33 (34%) received radiotherapy. Of those irradiated, 25% had treatment to the chest wall alone and 75% also received treatment to regional lymphatics. Systemic therapy comprised adjuvant chemotherapy (41%), tamoxifen 44%) and herceptin (2%). After a median follow up of 12 months, those who received radiotherapy had better 2 year disease-free survival 92% versus 53%. With the multiple variables involved it is difficult to determine whether it was selection or radiotherapy responsible for the statistically significant improvement in survival. Any true benefit of PMRT will only be demonstrated by large multicentre randomised trials which are long overdue.

Problems

- There have been no randomised controlled trials
- Balancing efficacy with compliance for ER+ve disease.
- AIs need to be combined with GnRH analogues.
- The benefit of adjuvant chemotherapy is unproven.
- PMRT is also unproven.
- Adequately powered multicentre RCTs are long overdue.

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Chapter 10
Treatment of Advanced Disease

Abstract In many series of MBC cases the majority had stage III/IV disease at presentation and this has shown little improvement with time. Historical methods of palliation involved ablative surgery including orchidectomy, adrenalectomy and hypophysectomy. The earliest form of additive therapy was estrogens, stilboestrol, ethinylestradiol and hexoestrol but these were associated with major side effects and were replaced by tamoxifen when this became available in the 1970s. Tamoxifen remains the most widely used palliative therapy for mMBC and comparative studies suggest that it is more effective than aromatase inhibitors. Approximately 15% of the estradiol is derived from the testis and when peripheral synthesis is there is a feedback surge of the testicular estrogen causing tumour stimulation. Multicentre studies are needed to determine the role of tamoxifen and gnRH analogues together with potential benefits of third line chemotherapy in selected cases.

A desperate disease requires a dangerous remedy. Guy Fawkes

Introduction

Because of the anatomy of the male breast and the frequent dysfunction of the male psyche there is often delay in presentation with consequent upstaging of MBC. The extent of the problem is shown in Table 10.1 which gives a breakdown of stage at diagnosis in the larger MBC series which have included all-comers [1–6]. The proportion of stage III/IV cases was between 32% and 79% indicating the large burden of advanced MBC. There was no evidence of a trend towards down-staging with time so that, at present, palliative treatment is being offered to the majority of men with advanced and metastatic male breast cancer (mMBC).

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Table 10.1 Stage at presentation in larger MBC series

Author	Country	N	Stage I	Stage II	Stage III	Stage IV
Ramantanis 1980 [1]	Greece	120	44 (37%)	37 (31%)	27 (22 (%)	12 (10%)
Ribeiro 1985 [2]	England	292	111 (38%)	61 (21%)	76 (26%)	44 (15%)
Gough 1993 [3]	USA	105	21 (20%)	27 (26%)	43 (41%)	14 (13%)
Yildirim 1999 [4]	Turkey	121	3 (2%)	35 (30%)	67 (55%)	16 (13%)
Bourhafour 2011 [5]	Morocco	127	6 (5%)	20 (16%)	64 (50%)	37 (29%)
Thuler 2014 [6]	Brazil	1189	170 (14%)	455 (38%)	406 (34%)	158 (13%)

Table 10.2 Effect of orchidectomy on metastatic MBC

Author	n	Response	No response
Treves 1959 [8]	41	28 (68%)	13 (32%)
Holleb 1968 [10]	38	17 (45%)	21 (55%)
Donegan 1973 [11]	6	4 (67%)	1 (33%)
Neifeld 1976 [12]	8	5 (62.5%)	3 (37.5%)
Meyskens 1976 [13]	70	47 (67%)	23 (33%)
Langlands 1976 [14]	14	14 (100%)	
Ribeiro 1976 [15]	8	0	8 (100%)
Ramantanis 1980 [1]	6	2 (33%)	6 (67%)
Everson 1980 [16]	13	6 (46%)	7 (54%)
Kraybill 1981 [17]	23	11 (48%)	12 (52%)
Kantarjian 1983 [18]	25	8 (32%)	17 (68%)
Patel 1984 [19]	22	11 (50%)	11 (50%)
Bezwoda 1987 [9]	6	2 (33%)	4 (67%)
Total	268	149 (56%)	67 (44%)

History

Because these cases were managed by surgeons, the initial hormonal therapies were ablative: orchidectomy, adrenalectomy, and hypophysectomy. In 1942 Farrow and Adair reported that a male with bone metastases responded to orchidectomy so this intervention became the standard of care for treatment of advanced disease [7]. The psychological impact of orchidectomy on a man who had already been diagnosed with what he believed to be a female disease has not been documented but is unlikely to have been very positive. Treves wrote "The acquiescence to orchiectomy seems to us to be a triumph of medical persuasion" [8] Bezwoda reported that orchidectomy was refused by 8/14 (57%) of men to whom it was offered [9]. Nevertheless castration was regarded as the treatment of choice for advanced/metastatic MBC and in studies reporting the results of orchidectomy overall, there was a 56% response rate, as summarised in Table 10.2 [8, 10–19]. It was not until 1977 however that the International Union against Cancer (UICC) outlined objective criteria for establishing response so that prior to this there was little uniformity in reporting outcomes of treatment.

Table 10.3 Response rates after adrenalectomy for metastatic MBC

Author	N	Response	No response
Huggins 1952/55 [20, 21]	2	2	0
Taylor 1953 [22]	2	1	1
Pyrah 1954 [23]	2	2	0
Douglas 1957 [24]	1	1	0
Cade 1958 [25]	2	?	0
Kolodziejsk 1962 [26]	1	1	0
McLaughlin 1965 [27]	2	2	0
Houttuin 1967 [28]	1	1	0
Holleb 1968 [10]	3	0	3
Li 1970 [29]	2	2	0
Eversson 1980 [16]	2	2	0
Ruff 1981 [30]	2	2	
Patel 1984 [19]	10	8	2

Adrenalectomy

The advent of cortisone meant that it was feasible to perform bilateral adrenalectomies without killing the patient. Only relatively few men have treated in this way but the some of the publications were written by famous mid twentieth century surgeons including Charles Huggins and Sir Stanford Cade. In 1952, Huggins reported the effect of adrenalectomy in an MBC case who had relapsed with lung metastases after orchidectomy [20]. Following bilateral adrenalectomies there was remission of disease. Subsequent publications are summarised in Table 10.3 which indicates the small numbers of cases with the largest series of 10 MBC reported by Patel et al. [10, 16, 19–30]. These historical results suggest that adrenalectomy was more likely than not to achieve a response in mMBC.

Hypophysectomy

If the data on response rates after adrenalectomy is sparse that relating to the effect of hypophysectomy is miniscule. None of the published series comprised more than 2 cases as is shown in Table 10.4 [10, 17, 31–35]. With the exception of the report by Luff, there was no evidence of response to hypophysectomy. Associated morbidity included diabetes insipidus, cerebrospinal fluid leakage, operative haemorrhage and meningitis

Because of these concerns about morbidity and lack of efficacy, additive rather than ablative hormonal therapies were introduced. These included high dose estrogens, progestins, antiandrogens, androgens, corticosteroids, and aminoglutethimide.

Table 10.4 Hypophysectomy for advanced MBC

Author	N	Response	No response
Luft 1957 [31]	2	2	0
Matson 1957 [32]			
Scowen 1958 [33]	1	0	1
Kennedy 1965 [34]	2	0	2
Holleb 1968 [10]	2	0	2
Cortese 1971 [35]	1	0	1
Kraybill 1981 [17]	2	0	2

Estrogens

In 1944 Alexander Haddow and associates reported a series of 22 patients with advanced breast cancer treated with the synthetic estrogen triphenylchlorethylene [36]. One case was a 54 year old male who had been treated with a radical mastectomy and radiotherapy but relapsed with skin and bone metastases. He was treated with 3 grams daily of triphenylchlorethylene for 3 months and the chest wall recurrences disappeared but he died after 6 months. Huguenin used the synthetic estrogen hexoestrol to treat 2 MBC cases and both responded [37]. Treves treated 13 advanced MBC cases with a variety of estrogens, (stilboestrol, ethinylestradiol and estradiol) with a response in 2 cases given ethinylestradiol [8].

A very encouraging result of stilboestrol therapy was reported by Ogilvie who described a 66 year old male who presented with a 25 cm fungating left breast cancer [38]. Treatment was started with 60 mg daily subsequently reduced to 15 mg daily. After 7 months there was a 9 x 20 cm indurated mass. This remained unchanged for 6 years with the patient being fit and well and still working. Reporting a series of 28 MBC cases, Donegan reported that there were 3 responses in the five men treated with oestrogens (4 stilboestrol 1 dienestrol) [11].

In a comparatively large series of 58 MBC cases with recurrent or advanced disease, Ribeiro used diethylstilboestrol and reported that of the 55 assessable cases there was an objective response in 14 and a partial response in 7 so that overall, the response rate was 38% [15]. Kraybill et al. administered stilboestrol to 2 cases of MBC, one of whom had failed to respond to provera and another who had responded but relapsed and this achieved a response for 4 and 14 months respectively [17]. Lopez et al. also used stilboestrol to treat 2 men with advanced MBC and obtained long remissions of 20 and 33 months [39]. Bezwoda reported that all the MBC patients given stilboestrol developed gynaecomastia and fluid retention [9]. Furthermore two had thromboembolism and another two developed cardiac failure. Such side-effects together with the emergence of less toxic endocrine therapies led to the gradual discontinuation of estrogen therapy for MBC (Table 10.5).

Table 10.5 Effect of estrogens on advanced MBC

Author	N	Agent	Response rate
Haddow 1944 [36]	1	Triphenylchlorethylene	100%
Huguenin 1951 [37]	2	Hexoestrol	100%
Treves 1959 [8]	5	Stilboestrol	0
	7	Ethinylestradiol	29%
	1	Estradiol	0
Ogilvie 1961 [38]	1	Stilboestrol	100%
Donegan 1973 [11]	5	Stilboestrol	60%
Ribeiro 1976 [15]	55	Stilboestrol	38%
Kraybill 1981 [17]	2	Stilboestrol	100%
Lopez 1982 [39]	2	Stilboestrol	100%
Kantarjian 1983 [18]	18	Estrogen not specified	17%

Table 10.6 Response of metastatic MBC to anti-androgens

Author	N	Antiandrogen	Response
Lopez 1985	10	CPA	70%
Doberauer 1988	5	Flutamide	80%
Di Lauro 2014	36	CPA ± buserelin	53%

Antiandrogens

Cyproterone acetate (CPA) is a steroidal antiandrogen with progestogenic and antigonadotropin properties. It acts by blocking the androgen receptor thereby inhibiting synthesis of androgens. As such it represents a possible alternative to orchidectomy. Lopez et al. treated 10 men who had recurrent/advanced MBC with CPA 100 mg twice daily [40]. Using UICC response criteria they reported that 7 (70%) responded for a median duration of 8 months (Table 10.6).

Flutamide is a non-steroidal anti-androgen which competitively blocks the androgen receptor. Doberauer used a combination of the gnRH analogue buserelin as a nasal spray and flutamide tablets 250 mg thrice daily to treat 5 men with advanced MBC [41]. There were 4 partial remissions lasting for a median of 15 months.

Di Lauro et al. treated 36 metastatic MBC cases with either CPA alone (14) or in combination with a gnRH analogue (22) [42]. The overall response rate was 53% and there were 4 complete responses and 15 partial responders. No response was seen in the 3 men whose tumours did not have androgen receptors.

Progestins

Progestins have been used often as second or third-line treatment. In 1961 Geller et al. reported an objective tumour response in a male with metastatic disease who was treated with delalutin (17-alpha hydroxy progesterone caproate) [43]. Results

Table 10.7 Response of metastatic MBC to progestins

Author	N	Progestin	Response rate
Geller 1961 [43]	1	Delalutin	100%
Kraybill 1981 [17]	5	MPA	60%
Lopez 1985 [40]	2	MPA	50%
Bezwoda 1987 [9]	8	MPA	37.5%
Doberauer 1988 [41]	1	MPA	0
Karakuzu 2006 [44]	1	Megestrol	0

of treatment with medroxyprogesterone acetate (MPA) and megestrol show great variation, probably because of different sequences of administration so that any potential effects may have been lost as a result of prior systemic therapy. Kraybill et al. used MPA as first-line treatment of mMBC in 3 men refusing orchidectomy and reported responses in 2, lasting for 3 and 10 months [17].

Lopez et al. administered synchronous chemotherapy (cyclophosphamide, methotrexate and vincristine CMFV to a 55 year-old with lung metastases with no response being observed [39]. A second 67 year old with bone metastases was treated with CMF and MPA which led to a partial response. Bezwoda used MPA as second line treatment in 8 cases and 3 responded, all of whom had previously received tamoxifen with some benefit [9]. Duration of response was between 4 and 7 months. After treatment with palliative CMF, in a patient with soft tissue and bone metastases Doberauer et al. administered MPA but unfortunately the disease progressed. Karakuzu et al. reported a 58-year-old who had rapidly progressive skin metastases from MBC and had previously received FAC and tamoxifen [44]. They used a combination of megestrol and external beam radiotherapy but were unable to control the disease. As salvage therapy in previously treated mMBC there appears to be little benefit from using progestins (Table 10.7).

Androgens

There are anecdotal reports of responses in mMBC using various androgens but these may be examples of publication bias. Donegan used fluoxymesterone (halotestin) in a 72-year old man who had relapsed with chest wall disease 7 months after radical mastectomy [11]. This achieved a partial response which lasted for 16 months. Horn and Roof reported 2 men who had relapsed after orchidectomy and were then given 7α, 17β-dimethyltestosterone (Calusterone) [45]. Both showed a response of bone and lung metastases for 5 months and 7 months. Reporting results from MD Anderson Hospital, Kantarjian et al. used androgens, type unspecified to treat 3 men with mMBC, 2 of whom had responded to prior orchidectomy and one of these had a second response [18]. The male who had not responded to orchidectomy also failed to respond to androgens.

Table 10.8 Treatment of advanced MBC with tamoxifen

Author	N	Response rate	Comment
Cantwell 1978 [46]	3	100%	
Patterson 1980 [47]	31	48%	CR/PR 15, SD 5
Becher 1981 [48]	2	100%	PR 1, SD 1 for 54 months
Ribeiro 1983 [49]	24	37.5%	CR5, PR4
Kantarjian 1983 [18]	8	25%	7 were not castrated
Lopez 1985 [39]	7	43%	
Bezwoda 1987 [9]	12	58%	5 responders ER+ve
Doberauer 1988 [41]	5	80%	SD4,PD1

Tamoxifen

The selective estrogen receptor modulator (SERM) tamoxifen has now been used extensively to treat advanced or metastatic MBC. From Guy's Hospital, Cantwell et al. were the first to report a beneficial effect [46]. All 3 patients responded, 2 for >1 year and the third for 10 months. This was followed by a flurry of publications, many of which were series comprising only one case. Patterson et al. treated 31 mMBC cases with varying doses of tamoxifen in a multi-centre study [47]. Complete or partial response occurred in 15 (48%) and 5 achieved static disease. In terms of site of metastatic disease site, for those with visceral dominant 5/10 responded compared with 2/5 (40%) with bone-secondaries and 8/15 (53%) with predominantly soft tissue-disease.

Becher et al. treated 2 men with tamoxifen after both had refused orchidectomy and one who had been heavily pre-treated had static disease for 54 months [48]. In a multicentre study 31 metastatic MBC cases were treated with tamoxifen and a complete or partial response was seen in 15 (48%), together with a further 5 who had stable disease.

Ribeiro et al. reported a series of 24 mMBC cases in which tamoxifen achieved a complete response in 5 and a partial response in 4 [49]. Of 8 cases treated at MD Anderson Hospital only 2 responded [18]. Bezwoda treated 12 cases of whom 58% responded and 5 were known to have ER+ve tumours [9]. Among 5 cases given tamoxifen of whom only one was known to be ER+ve, Doberauer reported static disease in 4 [41]. Results are summarised in Table 10.8.

Aromatase Inhibitors

Aminoglutethimide was originally used to inhibit adrenal steroid synthesis in combination with dexamethasone and later hydrocortisone to achieve what was deemed a medical adrenalectomy. Subsequently it was found that it was active only in postmenopausal women with breast cancer because it blocked the peripheral conversion

of androgens to estrogens by p450 aromatase. As a result of some benefit being observed in metastatic FBC, Lopez treated 5 men with metastatic MBC and 2 (40%) responded [39]. Harris et al. went on to treat 5 metastatic MBC cases with aminoglutethimide and hydrocortisone [50]. One patient had been previously orchidectomised and had a remission lasting for 14 months. The other 4 patients with intact testes did not respond. The combination of low efficacy and side effects led to a waning in popularity of aminoglutethimide.

The development of third generation aromatase inhibitors anastrozole, letrozole and exemestane spawned several adjuvant trials for FBC. In the first study ATAC (Arimidex tamoxifen alone or in combination), there was a significantly improved relapse-free survival and so naturally the hope arose that this could also be replicated in MBC. Giordano et al. treated 5 advanced MBC cases with anastrozole, all of whom had received prior tamoxifen [51]. Three had static disease for 4, 8 and 9 months and the other 2 cases showed progression while receiving anastrozole.

Italiano et al. described a 57 year old male who had been treated by mastectomy and adjuvant tamoxifen but subsequently developed lung metastases [52]. Tamoxifen was re-started and a 31 month remission ensues. On progression he started anastrozole with complete remission of disease. Others reported success with either anastrozole ot letrozole in single case reports [53–55]. In a larger series of 15 patients, all of whom had ER+ve metastatic disease a complete or partial response was achieved in 6 (40%) but 7 developed progressive disease [56]. More encouragingly, Visram reported a 60% response with anastrozole and 100% response following letrozole [57].

Zagouri et al. reviewed 23 mMBC cases of whom 17 received aromatase inhibitors with a GnRH analogue and 6 were given only an AI [58]. This was first-line therapy in 14(61%) and second-line therapy in 9 (39%) of patients, respectively. No grade 3 or 4 toxicity was reported. There was a partial response was observed in 6 (26 and static disease in 13 (56%). In this study no difference in overall survival was seen for those treated with or without GnRH analogue.

No study has directly compared tamoxifen with AIs as systemic therapy for MBC but in 2013 Eggemann et al. reported a large series of 257 males reported to German Cancer registries, of whom 260 received tamoxifen and 50 were treated with an aromatase inhibitor [59]. After a median follow-up of 42 months, after adjustment for age, tumour size, grade and nodal status, those treated with an AI had a 1.5-fold increased mortality rate compared with those given tamoxifen.

The explanation for this paradox has now emerged. In males approximately 15% of the estradiol is derived from the Leydig cells in the testis and the remainder of the plasma estradiol is the result of peripheral aromatisation of androgens [60–62]. When aromatase inhibitors are administered the peripheral synthesis stops but the feedback effect on the testis may, in time, produce more estrogen thereby causing tumour stimulation and loss of control (Table 10.9).

Table 10.9 Response of metastatic MBC to aromatase inhibitors

Author	AI	N	Response	Comment
Giordano 2002 [51]	A	5	60%	SD 3, PD 2
Italiano 2004 [52]	A	1	100%	CR
Zabolotny 2005 [53]	L	1	100%	CR 12 months
Arriola 2007 [54]	L	1	100%	
Carmona-Bayonas 2007 [55]	A	1	100%	Concomitant herceptin
Doyen 2010 [56]	A	15	40%	CR 2, PR, 4, SD 2, PD 7
Visram 2010 [57]	A L	5 5	3 (60%) 5 (100%)	
Zagouri 2013 [58]	A/L	6	3 (50%)	PR 3, SD 2, PD 1
Kuba 2016 [59]	L	3	2 (67%)	PR2, PD 1

CR complete response, *PR* partial response, *SD* static disease, *PD* progressive disease

Table 10.10 Response of metastatic MBC to fulvestrant

Author	N	Response	Comment
Agrawal 2007 [63]	2	100%	First line treatment
Rodrigues 2009 [64]	1	100%	Prior chemotherapy
Masci 2011 [65]	5	20%	PR 1. SD 2. PD 2
Zagouri 2013 [58]	14	21%	PR 3 SD 7 PD 4

Fulvestrant

Fulvestrant (7-alkylamide derivative of estradiol) has estrogen antagonistic activity but does not possess estrogen agonist effects. It binds competitively to estrogen receptors and degrades them in human breast cancer tissue. In 2007 Agrawal et al. reported 2 cases of mMBC both of whom had objective responses to first line fulvestrant [63]. De la Haba Rodrigues et al. described a further case who was 69 when he relapsed with lung metastases [64]. As adjuvant treatment he had previously received chemotherapy and tamoxifen. After diagnosis of metastatic disease he was treated originally with epirubicin, docetaxel and later capecitabine, all of which failed to halt the progress of the disease. He started fulvestrant and after 4 months his dyspnoea improved and radiologically, there was a partial response.

In a series of 5 patients reported by Masci et al., there was one partial response, 2 cases with stable disease and 2 who progressed, one of whom had low levels of ER and PR [65]. The largest series of 14 cases was reported by Zagouri et al. [58] and the outcomes of this cohort and the other reported cases are summarised in Table 10.10. Response was evaluated using RECIST criteria and none of the patients had received chemotherapy for advanced disease. Six received fulvestrant as second line endocrine therapy, 7 as third-line and 1 as fourth line. There was a partial response in 3 and static disease in 7 cases with a median time to progression of 5 months.

GnRH Analogues

Analogues of gonadotropin-releasing hormones (GNRH analogues) reduce gonadal steroidogenesis and 3 different agents, buserelin, leuprolide and goserelin have been used to achieve a reversible medical castration in mMBC. Vorobiof and Falkson reported the case of a 60 year male found to have pulmonary metastases at the time of mastectomy whom they treated with buserelin 2400 pg daily administered intranasally [66]. The patient reported hot flushes and loss of libido. After 3 months there was a complete response which was maintained for at least 11 months. Doberauer et al. treated a series of 10 mMBC cases with buserelin, 5 having the single agent and the other 5 also receiving the anti-androgen flutamide [41]. Of those given buserelin alone almost all had been heavily pretreated with both endocrine and cytotoxic therapy. The only one who had FAC alone went on to have a partial response lasting 12 months and on progression was also treated with flutamide achieving a second response lasting for 24 months. Three others had static disease and one progressed. Among the group given both buserelin and flutamide, 4 had partial responses lasting 4–16 months and one had progressive disease.

Using the combination of buserelin and the antiandrogen cyproterone acetate Lopez et al. treated 11 mMBC patients and 2 had complete responses lasting for 12 and 24 months [67]. There were 5 partial responses, 3 with static disease and 1 with progressive disease. Giordano & Hortobagyi combined leuprolide with aromatase inhibitors to treat 2 men with mMBC [68]. The first was aged 56 with pulmonary metastases who had previously received tamoxifen, anastrozole and exemestane and on progression he was given leuprolide and letrozole which achieved a partial response lasting for at least 5 months. The other patient was 49 and he had bone and lung metastases which had responded to capecitabine. On progression progression he started leuprolide acetate and anastrozole. There was a good partial response which lasted for >6 months.

Less encouragingly, Wong described a 56 year old with lung and bone metastases whose disease progressed with letrozole so he was switched to goserelin and exemestane and but did not respond [69]. This may have arisen as a result of his primary tumour being PR+ve but ER−ve.

In 2015 Di Lauro et al. conducted a meta-analysis of 60 MBC cases treated with monotherapy aromatase inhibitor or cyproterone (23) or in combination with a GnRH analogue (38) [70], The overall response rates were 43.5% and 51% respectively. Median overall survival durations were 30.1 and 22 months indicating the superiority of combination treatment with GnRH analogue.

Recently Kuba et al. reported 4 Japanese patients with mMBC, all of whom had previously received tamoxifen [71]. Three were treated with AI alone and one was given AI plus a GnRH. Two given AI alone responded, one with undetectable E2 levels and the other with detectable levels. Although the third had undetectable E2 nevertheless progression occurred although there was a response after starting a GnRH agonist. E2 concentrations were related to the efficacy of treatment in one patient. The patient initially treated with both AI and GnRH agonist also responded with no grade 3 or 4 adverse events experienced by any of the patients.

Table 10.11 Response of metastatic MBC to GnRH analogues

Author	N	Response (Duration)	Comment
Vorobiof 1987 [66]	B 1	100% (11 months)	Buserelin
Doberauer 1988 [41]	B 5 B + F 5	PR 1 PR 4	B alone had another PR after F
Lopez 1993 [67]	B + CA 11	CR 2 PR 5	
Giordano 2006 [68]	LEU + AI 2	PR 2	
Wong 2007 [69]	G + L	PD	ER−ve primary
Di Lauro 2015 [70]	AI/C 23 AI/C + GnRH 37	43.5% 51%	AI/C + GnRH prolonged survival
Kuba 2016 [71]	AI 3 AI +GnRH 1	PR 2 PR1	Response unrelated to E2 levels

B Buserelin, *F* Flutamide, *CA* cyproterone acetate, *LEU* Leuprolide acetate, *AI* aromatase inhibitor, *GnRH* gonadotrophin releasing hormone

Chemotherapy

Reports on the use of chemotherapy in advanced or metastatic MBC are relatively sparse and large series treated with state of the art chemotherapy are non-existent. Results are summarised in Table 10.11. In 1970 Li et al. described a patient with mMBC who had failed to respond to orchidectomy but who went into remission after adrenalectomy only to relapse 6 months later [29]. At that time he was treated with fluorouracil, methotrexate and thiotepa which led to a remission lasting for 18 months. Aisner et al. reported a patient with ER+ve mMBC who refused both orchidectomy and estrogens so he was treated with cyclophosphamide methotrexate and fluorouracil (CMF) but after 4 cycles it was evident that the disease was progressing [72]. Gupta et al. treated one mMBC case with chlorambucil without any response and another with CMF, leading to a transient response [73].

The MD Anderson group reported results from 18 mMBC patients who had received adequate doses of palliative chemotherapy and whose response rate was determined in a pre-defined manner [74]. The overall response rate was 44%. Of the cases, 6 had received no prior endocrine treatment and because of predominantly visceral metastases were given various combinations with partial responses observed after CMF, AC, C, bleomycin/vincristine, thiotepa and melphalan. Among those who had been pre-treated with endocrine therapy there was one complete response with fluorouracil and prednisolone which lasted for 13 months, and 6 partial responses (methotrexate 2, CAF 1, thiotepa/prednisolone 1, melphalan 1, CMF 1 and cyclophosphamide/prednisolone 1)

Kraybill et al. treated 6 males with mMBC which had progressed after orchidectomy with chemotherapy, cyclophosphamide (C), or cyclophosphamide and methotrexate (CM) or CMF [17]. There was no response to CMF but an overall 67% response to chemotherapy. Lopez et al. treated 14 men with palliative chemotherapy, using a variety of regimens including CMFVP and adriamycin combinations

and reported a 365% response rate [75]. In contrast Bezwoda et al. reported response rates of 60% to CMF and 80% to adriamycin and vincristine [9]. Doberauer treated 2 men with palliative CMF without a response and one with FAC who had a partial response that lasted for 12 months [41]. Crichlow reported 4 mMBC cases and partial responses were seen in 2 [76].

Doughty used a different approach in a patient with locally recurrent chest wall disease who had refused orchidectomy and systemic chemotherapy [77]. An angiogenic catheter was introduced via the lateral thoracic artery and after checking that this was perfusing the tumour nodules using patent blue dye, a combination of mitomycin-C, methotrexate and mitoxantrone (MMM) was infused and the procedure repeated thrice subsequently. The patient remained disease-free for 7 months later.

Tanaka treated a 79 year old who had nodal, bone and chest wall disease with a combination of fluorouracil, epirubicin and cyclophosphamide, together with tamoxifen for 5 cycles and then tamoxifen alone [78]. The chest wall disease was resected and the patient appeared disease-free 20 months later. Sato reported the successful salvage of a male suffering with massive intraperitoneal metastases using docetaxel, doxorubicin and cyclophosphamide (TAC) with a good partial remission after 4 cycles [79].

Using data from German Regional cancer Registries, Foerster et al. reported on 41 mMBC cases of whom 17 received palliative radiotherapy [80]. Interestingly, of the 30 that had HER2 status determined, 5 (17%) were HER2+ve, suggesting an over-representation of this phenotype among mMBC cases. No response rates were given for each regimen of which there were 6 different types because the study was not set up to examine this aspect. Anthracycline/taxane was the most frequently combination used in 10 cases (59%). After diagnosis of distant disease the median survival was 32 months, increasing to 68 months in those given systemic therapy (Table 10.12).

Lessons learned from chemotherapy trials in FBC are now being applied to mMBC although minimal published data are available. Anthracyclines are being used as first line chemotherapy and on progression taxanes are given as second line treatment provided that adjuvant chemotherapy had been used >12 months previ-

Table 10.12 Response of metastatic MBC to chemotherapy

Author	N	Regimen	Response
Li 1970 [29]	1	CMT	100%
Aisner 1979 [72]	1	CMF	0%
Gupta 1980 [73]	2	Chlorambucil, CMF	50%
Yap 1980 [74]	18	CMF,C, AC, CAF	44%
Kraybill 1981 [17]	6	C, CM, CMF	67%
Lopez 1986 [75]	14	CMFVP, A	35%
Bezwoda 1987 [9]	15	CMF (8) AV (5)	50%
Doberauer 1988 [41]	3	CMF (2) FAC (1)	33%
Crichlow 1990 [76]	4	C	2
Doughty 1995 [77]	1	MMM	100%

ously. For third and 4th line chemotherapy capecitabine and eribulin may be used. Giotta et al. reported a multicentre study of 23 Italian mMBC treated with eribulin for a median of 6 cycles [81]. There were 2 complete responses and in all other cases there was stable disease. Treatment was well tolerated with grade 3 adverse effects in only 4 patients and 8 (35%) having no side effects. For the patients who died the median overall survival was 65 months ((range, 22–228).Other options include platinum, vinorelbine and metronomic low dose chemotherapy to target tumour angiogenesis.

HER2+ve advanced disease needs first line treatment with trastuzumab, pertuzumab and docetaxel or alternatively trastuzumab and taxane. On progression Trastuzumab emtansine (Kadcyla®) may be used as second line salvage therapy. Depending upon resource allocation capecitabine and lapatinib represent a potential third line therapy.

The mTORC1 inhibitor everolimus (Afinitor/RAD001) was used by Brannon et al. to treat a 66 year old male who presented with an ER+ve, HER2−ve stage IIIA invasive cancer treated by mastectomy, chemotherapy, radiotherapy and tamoxifen [82]. When distant metastases were diagnosed he started a combination of BEZ235 200 mg twice-daily and everolimus 2.5 mg. There was stable disease of 18 months before progression. Samples were available from the primary and a metastasis. There were no markers of PI3K/mTOR pathway hyperactivation present in the first sample but there was more than fivefold increased ER and pathogenesis-related protein expression which possibly affected PI3K/mTOR pathway inhibition by BEZ235/ everolimus.

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Chapter 11
Prognosis

Abstract When properly matched for stage age and co-morbidity the prognosis of MBC and FBC is similar. Because MBC patients are older and often have more co-morbidity than FBC cases, overall survival may be worse but cancer-specific survival is similar. Ethnic differences in outcome are cultural and economic but not genetic. Hierarchical clustering indicates that best survival is exhibited by luminal B1.1 group and the worst by luminal A. *BRCA2* mutation carriers have a worse prognosis than that of sporadic cases. Oncotype Dx™ may be useful in determining recurrence risk and selected of appropriate adjuvant systemic therapy. Over-expression of both HIF-1a and plasminogen activator inhibitor 1 (PAI-1) have been shown on separate multivariate analyses to be significant prognostic variables. In contrast MBC tumours over-expressing TAZ/CTGF and YAP/CTGF carried a worse prognosis. Prognostic models developed for FBC cases can also be of value in MBC.

Prediction is very difficult, especially if it's about the future. Nils Bohr

Males Versus Females

Considerable energy has been devoted to the question "Is male breast cancer inherently more aggressive than the female disease?" After all this frenetic activity it emerges that there is not an inherent disadvantage of being a male with breast cancer. The major problem was the lack of good matching, particularly for stage because of the male habit of presenting with more advanced cancers. The studies which have compared 5 year survival of MBC and FBC are summarised in Table 11.1.

Examining the breast cancer registry of the Philadelphia County Medical Society Mausner et al. reported that between 1951 and 1964, 9003 patients were recorded [1]. They took a 10% random sample of 830 FBC cases and compared their characteristics with 72 MBC cases. The males were significantly older with a mean age of 64, compared with 56 for the females. There was also a substantial increase in male delay being more than a year in one third of MBC and one fifth of FBC. There was a slightly worse 5-year observed survival for males with stage I and II disease, but no gender difference in relative 5-year survival. Using data from the Cancer Registry

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Table 11.1 Comparative studies of overall survival in male and female breast cancer

Author	Country	MBC No	MBC 5y OS	FBC No	FBC 5y OS
Mausner 1969 [1]	USA	Stage 1 34 Stage II 24	65% 43%	Stage I 442 Stage II 339	76% 48%
Levi 1992 [2]	Switzerland	39	75%	4199	71%
Willsher 1997 [3]	England	41	55%	123	65%
Scott-Conner 1999 [4]	USA	Stage I 442 Stage II 536	78% 68%	Stage I 358 Stage II 411	85% 70%
Giordano 2004 [5]	USA	Stage I 394 Stage II 516	76% 67%	Stage 1 80,657 Stage II 63.988	88% 75%
El-Tamer 2004 [6]	USA	53	74%	53	74%
Anan 2004 [7]	Japan	14	92%	140	86%
Macdonald 2005 [8]	Canada	RT 34 No RT 26		RT 939 No RT 3242	
Nahleh 2007 [9]	USA	Stage I 138 Stage II 241	40% 40%	Stage I 745 Stage II 703	60% 54%
Marchal 2009 [10]	France	58	59%	116	68%
Anderson 2009 [11]	USA	5496	1976–1985 79% 1986–1995 85% 1996–2005 90%	835,803	1976–1985 75% 1986–1995 85% 1996–1905 90%
Foerster 2011 [12]	Germany	108	71%	108	70%
Nilsson 2011 [13]	Sweden	99	54%	396	80%
Shaaban 2012 [14]	UK	251	87%	263	75%
Chen 2013 [15]	China	150	66%	300	75%
Kwong 2014 [16]	Hong Kong	132	79%	8118	78%
Iorfida 2014 [17]	Italy	99	89%	198	92%
Yu 2015 [18]	China	91	80%	Postmeno 182 Premeno 182	80% 75%
Yu 2015 [19]	Canada	37 38	Node –ve 95% Node +ve 79%	580 733	Node –ve 92% Node +ve 73%
Choi 2016 [20]	Korea	260	91%	1300	93%

of the Swiss Canton of Vaud Levi et al. compared crude and relative survival rates for 39 MBC and 4.199 FBC cases [2]. The relative survival rates were 0.95 and 0.94 respectively. For males, relative survival was not significantly affected by age.

Wilsher et al. compared 41 MBC with 123 FBC, matched for age, tumour size, grade and nodal status [3]. The matching for the latter very important variable could not be achieved since the axillary nodal status was unknown for 23 (56%) of the MBCs. In this study there was a worse 5 year survival among the male cases. Scott-Conner et al. examined the National Cancer Data Base with 4755 MBC and 624,174 FBC diagnosed between 1985 and 1994 [4]. An attempt was made to select for each

MBC an FBC case matched for age, ethnicity, economic status and tumour stage and this was successful in identifying 3627 matched pairs. Surgery involved mastectomy in 65% of males and 55% of females. Post-mastectomy radiotherapy was given to 29% of men and 11% of women. For patients with stages I/II 5 year survivals were similar but there was worse outcome for males with stage III and IV disease.

Giordano et al. interrogated the SEER register of breast cancer cases identified between 1973 and 1998 database were used [5]. There were 910 MBC and 144,645 FBC. In terms of adverse prognostic factors, males had a higher incidence of advanced stages and axillary nodal involvement. When matched for stage the relative survival was similar for males and females. Using the Columbia/ Presbyterian Medical Center database, El-Tamer et al. identified 53 MBC cases and compared their outcome with 53 FBC who had been matched for both age and date of diagnosis, together with stage and histology [6]. The 5-year overall survival for both males and females was 77%. When however the cancer-specific survival curves of the two gender groups were compared, at 5 years it was 81% for females and 90% for males and the respective figures after 10 years were 70% and 90%.

In a relatively small study from Japan, Anan et al. examined the 5-year OS of 14 MBC with that of 140 age and stage-matched FBC [7]. There was no significant difference in OS which was 92% for the males and 86% in the females. Disease-free and overall survival did not differ significantly between the sexes. Five-year disease-free survival was 77% for the men and 75% for the women. There was however an increased mortality in males from other causes probably reflecting the male preponderance of comorbidity.

Approaching the problem from a clinical oncological perspective, Macdonald et al. from the British Columbia Cancer Agency sought to determine the prognostic significance of post-mastectomy radiotherapy (PMRT) in MBC and FBC [8]. The study included all cases of invasive breast cancer between 1989 and 1998 and there were 60 MBC and 4181 FBC. PMRT was more likely to be given to those with larger cancers, involved margins, nodal involvement and male gender. Using the Veterans Affairs Central Cancer Registry (VACCR) Nahleh et al. examined the outcome for 612 MBC patients and 2413 FBC cases [9]. The males were on average 10 years older than the females (67 versus 57 $P < .005$). The median overall survival was 7 and 9.8 years respectively ($P < .005$). For node-negative patients, the median survival rates were 6.1 and 14.6 years ($P < .005$). In contrast, the overall survival of node positive showed no gender difference.

Marchal et al. conducted a case-control study with 58 MBC and 116 FBC, matching for age, stage and year of diagnosis [10]. For MBC the 5 and 10-year OS was 59% and 34% compared with 68% and 52% in females. Although males had an increased likelihood of dying from other diseases, the disease-specific survival of both genders was similar. Anderson et al. analysed SEER data from 1973 to 2005 which included 5494 MBC and 835,805 FBC cases [11]. When cases diagnosed between 1976–1985 were compared with those treated from 1996–2005, after adjusting for age, stage, and grade there was a decline in cause-specific mortality of 28% in males and 42% in females.

In a matched pair analysis of German MBC and FBC, 108 cases were compared after controlling for year of diagnosis, age, stage, nodes, grade, and ER/PR/HER2 status [12]. The 5-year OS was 71% for males and 70% in females. Nilsson et al. carried out another case-control study with 99 MBC cases and 396 FBC controls, matched for age and year of diagnosis [13]. There was inferior OS in males (41% versus. 55%) and also worse relative survival (74% versus 88%, p = 0.015)

Shaaban et al. performed a large scale biomarker study and compared survival of 251 MBC and 263 FBC with matching for age, grade, and nodal status [14]. There were no significant gender differences in OS at 10 years. Chen et al. compared 150 MBC patients with 300 stage-matched FBC cases [15]. The mean ages at diagnosis were 59 years for males and 57 for females. The 10-year overall survival rates were 54% and 69% respectively (P = 0.002).

Kwong et al. reported different findings in a Chinese case-control study of 132 MBC and 396 FBC cases [16]. Mean ages at diagnosis were 65 (male) and 53 (female). Because of lack of matching MBC were of lower grade, stage, size, and more likely to be ER+ve. The 5 year OS for males was 79% and 78% for FBC. Males were however more likely to die of other causes. Males had better disease-specific mortality rates at all ages ($p < 0.01$).

Reporting from the European Institute of Oncology Iorfida et al. examined the outcomes of 99 MBC cases and 198 FBC, matched for age, stage, grade, year of surgery, and ER/HER2/Ki67 status [17]. The 10-year OS was 71% (MBC) and 84% (FBC). There was a significantly increased risk of non-cancer related deaths among the males but the 10-year disease-specific survival of the two gender groups was similar (82% versus 88%). In another Chinese case control study, Yu et al. compared the survival of 91 operable MBC cases with 182 pre/perimenopausal FBC and another 182 postmenopausal cases who had been treated at Zhejiang Provincial Cancer Hospital [18]. After a median follow-up of 112 months, the 10-year OS rates were 79% for MBC, 79% in the pre-perimenopausal FBC and 88% in postmenopausal FBC cases. It was concluded that MBC had a similar survival to premenopausal FBC but a worse outcome compared with the post-menopausal.

FBC. However, the DFS and OS values of MBC were similar to those of pre/peri-menopausal FBC and were worse than were those of post-menopausal FBC.

A Canadian study compared 75 operable MBC cases with 1313 FBC [19]. They used propensity score matching (PSM) in an attempt to estimate the effect of a treatment after accounting for the covariates that predict receiving the treatment and reduce the inherent biases in non-randomised studies. The median follow-up was 90 months and after PSM there was reasonable balancing of prognostic variables in the MBC and FBC cases. The 10-year survival for node negative MBC and FBC was 39% and 85% respectively. Among the node positive cases the respective 10-year survival rates were 34% and 49%. The 10-year cancer specific survival rates for node negative cases were 54% and 85% and for the node positive patients 55% and 56%. Recently Choi et al. examined OS in 400 Korean MBC cases and compared this with that of matched FBC patients [20]. Each MBC had 5 FBC controls and after matching for stage and ER status, there remained 260 MBC and 1300 FBC. The respective 5-year OS rates were 91% and 93%. On multivariate analysis the only significant prognostic variables in MBC were age >60 and tumour.

Age

In a joint Scandinavian project, 1429 MBC cases were studied with regression analysis of annual relative survival rates [21]. What emerged was a lower relative survival rate in older patients. During the first 5 years of follow-up the relative excess risk of death from breast cancer increased more than threefold compared with those aged <40 years at diagnosis. There were significantly higher mortality rates in Denmark and Finland, compared with Sweden which may have been due to later presentation.

Between 1933 and 1983, 124 MBC cases were treated at the Mayo Clinic [22]. Median follow-up was 6.7 years. There was a positive family history of breast cancer in 30 (27%) and 9 (7%) had previous chest wall irradiation. The 5-year disease-free survival (DFS) was 64%. Overall survival was 57% at 5 years and 31% at 10 years. Apart from the usual adverse factors: tumour size, nodal status and tumour grade, pain and increasing age were significantly associated with decreased survival.

Ioka et al. used the Osaka Cancer Registry data to examine 5-year survival of 97 MBC and 19,772 FBC cases diagnosed between 1975 and 1997 in Osaka Prefecture or between 1993 and 1997 in Osaka City [23]. MBC comprised approximately 0.5% of all breast cancer cases. The relative survival for males and females were 82% and 71% respectively. Figure 11.1 shows the relative survival of males and females according to date of diagnosis. Although there was a fairly steady state in FBC there was a substantial improvement in survival of MBC with time. Survival in older males was worse and this was associated with an increased proportion of advanced cases.

Tural et al. reported outcomes for 99 MBC patients treated in Istanbul between 1972 and 2011 [24]. They split the cases into two age groups: younger (<65) and older (≥65).

Although the older patients had larger tumours these were more likely to be ER and PR+ve. The 10-year OS was 56% in younger men compared with 49% for older patients. On multivariate analysis tumour size and axillary nodal involvement were significant indicators of prognosis.

Using the National Cancer Database, Sineshaw et al. investigated outcome in males aged 18–64 and ≥65 at the time of diagnosis [25]. The study group consisted

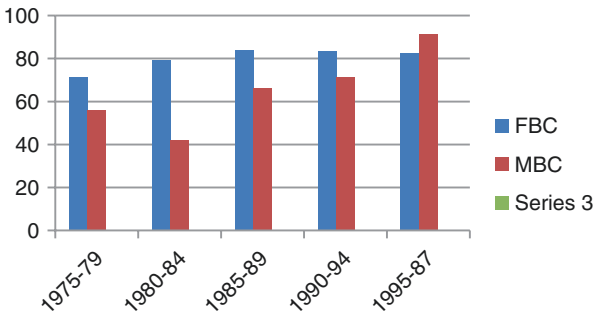

Fig. 11.1 Relative survival of FBC/MBC with year of diagnosis [23]

of 5247 white and 725 black patients with operable MBC. In both age groups treatment was given similarly to both ethnic groups but among those aged ≥65, chemotherapy was given less frequently. For white men the treated proportions were 79% and 42% as compared with 77% and 39% in black MBC cases. Mortality in younger black men was 76% higher than in the comparable white men when adjustment was made for clinical variables but fell to 37% becoming non-significant after adjustment for socio-economic factors.

Because of the problems of an excessive number of potential prognostic variables, Shahraki et al. used the LASSO method (Least Absolute Shrinkage and Selection Operator) to examine prognosis [26]. This constrains the absolute value of the regression coefficients, so that many diminish and some fall to zero. Such an approach is particularly applicable to MBC where the number of variables exceeds the sample size. They analysed 50 Iranian MBC cases with both Cox proportional hazard and LASSO-Cox models, fitted for 20 variables. Because the relative efficiency of LASSO-Cox was 22.29 times greater than the Cox model this eliminated 8 low strength variables. The most important variables to emerge after 19 years follow-up were age, alcohol consumption, laterality, nipple discharge, tumour grade and symptom duration. The finding that tumour laterality was a significant prognostic variable does appear somewhat counter-intuitive but the worse outcome for men with left sided cancers may have resulted from cardiac irradiation.

Breast cancer is exceedingly rare in male adolescent and young adults (aged between 15 and 39 years). Flaherty et al. examined the National Cancer Data Base for years 1998–2010 and identified 677 MBC cases of whom 122 (18%) had DCIS and 555 (82%) were diagnosed with invasive disease [27]. Factors associated with reduction in overall survival were age, ethnicity and socio-economic status. Those aged ≤25, of black race and who were uninsured all had significantly worse survival. As well as the established TNM variables, not having any surgery, or omission of nodal evaluation impacted significantly on survival. On multivariate analysis the two significant variables which emerged were age ≤25 years (HR 3.064, 95% CI 1.216, 7.720) and lack of evaluation of nodal status (HR 3.070, 95% CI 1.423, 6.626). The lesson to be learnt is that the very young do badly but age *per se* should not be an excuse for under-treatment.

Marital Status

Leone et al. investigated 2992 MBC cases diagnosed between 2003 and 2012 and registered on the SEER database [28]. In a multivariate analysis, the factors adversely affecting OS were older age, higher tumour grade, ER−ve cancer stage IV disease, being unmarried and not receiving surgery or radiotherapy. These findings suggest that vulnerability to worse outcome for MBC is increased by age and possibly as a result of isolation from living without a significant other.

In another SEER derived study (1990–2011), Adekolujo et al. examined the effect of marital status on stage at diagnosis and outcome in 3761 MBC cases [29]. Only those aged ≥18 years were included with marital status dichotomised to mar-

ried or unmarried (single, divorced, separated and widowed). Kaplan-Meier method was used to estimate the 5-year cancer-specific survival. Multivariate regression analyses were done to determine the effect of MS on presence of Stage IV disease at diagnosis and on cancer-specific mortality. The study included men; 2647 (70.4%) were married. Unmarried men were more often diagnosed with Stage IV MBC compared with married (10.7% vs. 5.5%, $p < .001$). Unmarried men (compared with married) were significantly less likely to undergo surgery (92.4% vs. 96.7%, $p < .001$). Overall unmarried males with Stages II, III, and IV MBC had significantly worse 5-year cancer-specific survival compared with married men. On multivariate analysis, being unmarried was associated with increased hazard of death (HR = 1.43, $p < .001$) and increased likelihood of Stage IV disease at diagnosis (OR = 1.96, $p < .001$). Unmarried males with breast cancer are at greater risk for Stage IV disease at diagnosis and poorer outcomes compared with married males.

Ethnicity

Keller from the US Veterans Administration collected 181 biopsy-confirmed MBC cases and two groups of male controls selected by terminal claim digits from a 1961 hospital discharge claim-number listing [30]. Controls were matched for age within 5 years, and either for place of residence or type of hospital. One control group (non-cancer) had non-malignant diagnoses and the other cancer control group had been treated for bladder or kidney cancer. When the 7 year overall survival rates of white and black males were compared they were 35% and 46% respectively. This suggested that, among those having access to good medical care through the Veterans Administration, there was no major difference in outcome based on ethnicity.

Brenner et al. collected 131 MBC cases diagnosed at two medical centres on Israel between 1960 and 2000, together with a further 470 reported to the Israel Cancer Registry from 1980 to 1997 [31]. Of the 131 Jewish patients seen at Rambam and Rabin hospitals, 102 (78%) were Ashkenazi and 29 (22%) Sephardic. Although both groups had similar clinical characteristics there was significant more comorbidity in the Sephardim with a trend towards younger age and higher stage at the time of diagnosis. This was associated with significantly worse prognosis. Analysis of the Cancer Registry cases showed an 80% increase in the risk of developing MBC among the Ashkenazim. There was however a worse prognosis for the Sephardim with estimated 5-year survival rates of 62% versus 64% in the Ashkenazim.

O'Malley et al. used SEER data to examine survival rates in 1979 MBC cases reported between 1973 and 1997 in relation to ethnic origin: non-Hispanic white, non-Hispanic black, and other (mostly Asian/Pacific Islander and Hispanic) [32]. They used two endpoints: all-cause and breast cancer specific mortality. Because there were significant differences in survival of each ethnic group, subsequently individual group analysis was performed. The overall 5-year survival rate was 66% for whites, 57% for blacks, and 75% for men of other ethnicity. Black men were more likely to be diagnosed with more advanced disease. Within tumour stages there was worse survival for both black and white men compared with others. Other

prognostic factors such as age, use of surgery or radiotherapy were apparent but not always significant in all ethnic groups.

In another SEER study Crew et al. found 510 MBC cases aged ≥ 65 years with stage I-III disease diagnosed between 1991 and 2002 [33]. Of the cases 456 (89%) were white and 34 (7%) black, with 479 (94%) undergoing mastectomy, 143 (28%) being given adjuvant chemotherapy, and 148 (29%) having radiotherapy. Black men were half as likely to have consultation with an oncologist and receive adjuvant chemotherapy; however, the results did not reach statistical significance. Their outcome was worse with a cancer–specific mortality hazard ratio of 3.29 compared with white men.

O'Brien et al. were interested in differences in survival of MBC cases in relation to sociodemographic status and examined the outcome of 1589 males registered with the Florida Cancer Data System between 1996 and 2007 [34]. The 5-year overall survival was 66% with a mean survival time of 7.7 years. For white males the mean survival was 7.8 years, compared with 5.9 in black men. Non-Hispanic males fared worse than Hispanic men with mean survival of 7.7 and 8.5 years respectively. Those with the lowest socioeconomic status survived for an average of only 5.9 years compared with 8.2 years in the highest SES. Patients with low SES presented with more advanced cancers, 57% versus 48% for middle-high SES and 51% for the highest SES. In univariate analysis middle high and highest SES had better survival than those with lowest SES but this advantage disappeared on multivariate analysis. Significant prognostic variables for survival were marital status, age, smoking, tumour stage, treatments, and comorbidity. This indicates that any apparent ethnic differences in survival are largely economic, not genetic (Table 11.2).

Further evidence of the impact of socioeconomic status on prognosis of MBC came from the work of Shi et al. who examined the survival of 8828 American patients in relation to their payer status [35]. The patients were registered on the National Cancer Data Base and diagnosed between 1998 and 2006 with follow-up to 2011. Payer status was categorised as private 48%, Medicare 43%, Medicaid 3%, unknown 3%, and uninsured 3%. Median overall survival (MOS) for all patients was 10.6 years. In multivariate analysis, Direct adjusted MOS was 12.46, 11.89, 9.99, 9.02, and 8.29 years for private, "unknown," Medicare, uninsured, and Medicaid payer's status, respectively. Patients with private and "unknown" payer's status showed a significant difference in survival compared with uninsured patients, while Medicaid and Medicare patients did not. Age, race, stage, grade, income, comorbidity, distance travelled, and diagnosing/treating facility were also significant predictors of survival. Treatment delay and cancer program did not have a significant influence on survival.

Table 11.2 Survival of MBC cases in relation to ethnicity

	White		Black	
Author	N	5 yr. OS	N	5 yr. OS
O'Malley 2002 [32]	1613	66%	226	57%
Crewe 2007 [33]	456	90%	34	70%
O'Brien 2015 [34]	1437	75%	134	55%

Molecular Profile

In order to achieve more accurate classification and prognosis of MBC cases the techniques of molecular profiling used for FBC have been applied with varying degrees of success and agreement. At the Mayo Clinic, 111 MBC cases were treated between 1950 and 1992 and of these 77 had material suitable for immunohistochemical analysis [36]. The pattern of expression of estrogen, progesterone, androgen receptors (ER, PR, AR), together with *bcl*-2, p53, HER-2/*neu*, cyclin D1, and MIB-1 were determined. The majority of tumours were hormone receptor positive, ER (91%), PR (96%), AR (95%). The apoptosis inhibitor *bcl*-2 was expressed in 94% of cases. The proliferation marker MIB-1 was expressed in 38% and associated with a worsening of 5-year disease-free survival, DFS (43% versus 83%) as shown in Table 11.3. In contrast, expression of the cell cycle regulator cyclin-D was associated with a better 5-year DFS. There was positive staining for p53 in 21% and a strong association with cyclin D positivity.

Wang-Rodriguez et al. examined the expression of ER, PR, MiB-1, Her-2, and p53 in tumours from 65 MBC cases derived from the Veterans Administration Cancer Registry [37]. They conducted a case-control study with 17 age-matched male controls with gynaecomastia for each MBC case. The most important prognostic variable was the clinical stage irrespective of tumour size or lymph node status. MiB-1 and PR positivity were unrelated to prognosis but both HER-2 and p53 were associated with reduction in DFS.

Using DNA microarrays comprising 534 genes, Sorlie et al. categorised FBC into five subtypes: luminal A, luminal B, HER2 over-expressing, normal and basal [38]. Subsequently Nilsson et al. showed that a panel of four antibodies to ER, HER2, and cytokeratin 5/6 accurately identified MBC tumours with high specificity and greater simplicity [39]. The immunohistochemical pattern of staining to delineate the subtypes of MBC is shown in Table 11.4.

Table 11.3 Prognosis of MBC in relation to MIB-1 and cyclin D expression [36]

Marker			5 year disease-free survival
MIB-1	+ve	38%	47%
	−ve	62%	83%
Cyclin-D	+ve	58%	77%
	−ve	42%	53%

Table 11.4 Immunostaining of molecular subtypes of MBC (Nilsson 2013) [39]

Luminal A (87%)	Luminal B (11%)	HER2 (<1%)	Basal (2%)
ER+ve PR+ve	ER+ve PR+ve	ER+ve PR+ve	ER−ve PR−ve
ER+ve PR−ve	ER+ve PR−ve	ER+ve PR−ve	
ER−ve PR+ve	ER−ve PR+ve	ER−ve PR+ve ER−ve PR−ve	
HER2−ve	HER2−ve	HER2+ve	HER2−ve
Ki67 ≤15%	Ki67 >15%	Any Ki67	Any Ki67

Carrying this work forward, Ge et al. immunostained tumours from 42 MBC cases to determine the expression of ER, PR, cytokeratins 5/6 (CK5/6), EGFR, and NF-κB [40]. They reported that the luminal A subtype was the most frequent group found in 35/42 (83%) tumours. The second most common was which was luminal B subtype 7/42 (17%). There were no basal or HER2 subtypes identified.

Kanthan et al. measured tumour expression of cell cycle proteins in 75 MBC cases using IHC to assess proliferating cell nuclear antigen (PCNA), Ki67, p27, p16, p57, p21, cyclin-D1 and c-myc [41]. Overexpression of PCNA was inversely related to Ki67 expression which in most cases was negative. There was reduction in DFS in men with cancers that overexpressed PCNA. There was overexpression of cyclin D1 in 63 (84)% of cases. Cyclin D1 positive tumours were associated with significantly prolonged DFS. Overexpression of c-myc occurred in 68 (90%) and was associated better DFS, and so did p27 over expression whereas P21 and p57 positive tumours carried a worse prognosis. Although there was overexpression of p16 in 57 (77%) this did not significantly affect prognosis. These findings suggested that cyclin dependent kinases (CDK) might provide a new therapeutic approach for MBC.

Nilsson et al. studied 197 archival specimens from 197 MBC patients using IHC staining of tissue microarrays, together with standard histological grading [42]. To classify the specimens into molecular subtypes they used three different definitions: five biomarkers, biomarkers plus Nottingham histological grade (NSG) and biomarkers plus Ki67. The criteria are shown in Table 11.5. Using five markers, luminal A comprised 81% and luminal B in 11% compared with 48% and 44% with NSG and 41% versus 42% when incorporating Ki67. There were two basal-like tumours and no HER2 lesions. Irrespective of classification there was no detectable difference in prognosis of luminal A and B subtypes.

Studies of FBC had suggested that mutations including chromosome 17 centromere (CEP17) duplication, HER2 and/or Topoisomerase II alpha (Topo II-a) gene were associated with poor prognosis. This did however confer increased sensitivity to anthracycline-based chemotherapy. Schildhaus et al. used FISH and

Table 11.5 Different classifications of MBC (Nilsson 2013) [42]

Classification	Subtype	ER/PR	HER2	NHG	Ki67	CK5/6 EGFR
5 biomarkers	Luminal A Luminal B HER2 Basal	ER±PR+ ER±PR+ −ve −ve	−ve −ve +ve −ve	N/A N/A N/A N/A	N/A N/A N/A N/A	Any Any Any CK5/6+ve±EGFR+ve
Biomarkers + Nottingham grade	SNP Luminal A Luminal B	−ve ER±PR+ ER±PR+	−ve −ve HER2+ve ±NHG+ve	N/A N/A IHC	N/A N/A N/A	N/A N/A
Biomarkers + Ki67	Luminal A Luminal B Luminal HER2	ER±PR+ ER±PR+ ER±PR+	−ve −ve +ve	N/A N/A N/A	Low High Any	N/A N/A N/A

IHC on tumours from 96 MBC cases to identify molecular subtypes together with CEP17, HER2 and Topo II-a mutations [43]. What emerged was the rarity of HER2 amplification (6, 6.3%) and Topo II-a amplification or deletion (3, 3.1%). Furthermore CEP17 polysomy was present in only 9 tumours (9.4%) of tumours. HER2, Topo II-a and CEP17 gene alterations were unrelated to outcome. For men with luminal A tumours that were node negative there was a significant improvement in prognosis compared with node negative luminal B cases (5-year OS 100% versus 67%).

Abreu et al. carried out histopathological review of 111 Portuguese MBC cases and used IHC to determine ER, PR, AR, HER2, together with ki67 and p53 [44]. The 5 biomarker and 5 biomarkers + Ki67 were used to define subtypes using hierarchical clustering. Using both definitions the majority of MBC were luminal A (89% versus 60%) and with luminal B comprising (7% and 36%). Again, the basal-like phenotype was uncommon (3% and 3%) and HER2 was rare (<1%) using both classifications. There was no significant difference in outcome for luminal A and B cases using either classification ($p > 0.20$). Hierarchical clustering identified different prognostic sub-groups: A, B1.1, B1.2, B2 and C. There was only one member of group C and the characterisation of the other groups together with median survival is shown in Table 11.6. Multivariate analysis revealed that the best survival was exhibited by B1.1 group and the worst by group A.

Table 11.6 Clustering groups and prognosis [44]

	A	B1.1	B1.2	B2
N	4	14	66	6
ER+ve				
PR+ve				
AR+v				
HER2+ve				
Ki67 low				
P53 low				
Median survival	4.5	11.5	10.3	4.9
(years)				

Blocks represent % positivity

Table 11.7 Frequency of triple negative and HER2 phenotypes in MBC

Author	N	Triple negative		HER2	
		N (%)	Survival	N (%)	Survival
Arslan 2012 [45]	148	7 (5%)		35 (24%)	
Kornegoor 2012 [46]	134	5 (4%)		0	
Ottini 2012 [47]	382	14 (4%)		8 (2%)	
Schildhaus 2013 [43]	96	3 (3%)	Median 26	0	
Aggarwal 2014 [48]	51	1 (2%)		1 (2%)	
Leone 2015 [28]	960	28 (3%)		6 (1%)	
Gogia 2015 [49]	76	14(19%)		21 (28%)	
Abreu 2016 [44]	111	1 (1%)		9 (8%)	
Gargiulo 2016 [50]	47	3 (7%)	67%	13 (27%)	85%

Triple Negative

There is very little information on prognosis in relation to HER2 tumours or triple negative (TN) cancers because of the rarity of both. Frequency of these phenotypes in MBC series is shown in Table 11.7 [28, 44–50]. Triple negative tumours comprised 1–7% of the total except in the study of Gogia et al. with 19% of this phenotype [49]. This may have arisen because of a particular ethnic mix of patients or possibly laboratory problems with standardisation. Schildhaus reported a median survival of 26 months for TN cases compared with 90 months for those with luminal A tumours and 44 months for luminal B [43]. In the series of Gargiulo there were 3 males with TN cancers of whom one died after a median follow-up of 89 months. These scanty data hint of a worse outcome for MBC cases with TN cancers.

HER2

Since amplification of HER2 receptor had been found in >30% of FBC and was associated with a poorer prognosis, Blin et al. assayed 38 MBC samples to determine the frequency of over-expression and the potential prognostic impact value of this factor [51]. Although HER2 receptor was present in 36/38 specimens, there was no association between either tumour grade or prognosis. In a comparative study of 58 MBC and 202 FBC samples, Bloom et al. carried out IHC for HER2 receptor together with FISH to detect gene amplification [52]. Only 1 MBC (1.7%) showed amplification of HER2 compared with 52 (26%) of the FBC cases. Barlund et al. studied 128 MBC specimens by IHC and FISH and found that that amplification of HER2, MYC. PPM1D and ZNF217 was rare, being present in only 1–2% of cases [53].

HER2 phenotype is a rare component of MBC in most studies except those of Arslan [45], Gogia [49] and Gargiulo [50] which reported 24%, 28% and 27% respectively despite those with equivocal staining being analysed by FISH. With a

modal incidence of 2% no conclusions can be drawn concerning HER2 positivity and survival. It is likely however that most oncologists will recommend adjuvant herceptin and chemotherapy for such cases.

Oncotype DX_{TM}

Oncotype DX™ is a reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay capable of measuring expression of 21 tumour-related genes in archival paraffin-embedded specimens. The aim is to subdivide node negative cancers into low, intermediate and high risk of recurrence so that appropriate adjuvant therapy can be selected. Using material from 668 FBC patients enrolled in NSABP trial B14 (adjuvant tamoxifen versus placebo), Paik et al. selected 16 cancer related genes to derive a range of possible recurrence scores from 0 to 100 with risk of recurrence increasing with magnitude of the score [54]. They reported that 51% of cases were low risk (<18), 22% intermediate (18–30) and 27% high risk (≥31). Estimated 10-year distant recurrence rate in the low risk group was 7% compared with 14% for intermediate cases and 31% in the high risk group. In multivariate analysis, the prediction provided by the recurrence score provided was independent of both age and tumor size and also predicted overall survival.

Kiluk et al. from H Kee Moffit Cancer Center reported 3 MBC patients whose tumours were subjected to Oncotype Dx™ breast cancer assay [55]. Of these 2 proved to have intermediate recurrence scores and were advised to receive adjuvant chemotherapy. The third patient had a low risk score and received adjuvant endocrine therapy. Yokoyama et al. reported use of Oncotype DX™ in 60-year-old Japanese MBC case who had micrometastases in a sentinel node [56]. The low recurrence score of 8 enabled the clinicians to select tamoxifen rather than chemotherapy as adjuvant treatment.

In a large series of 65 Israeli MBC patients Grenader et al. reported that 29 (45%) were low risk, 27 (42%) intermediate and 9 (14%) high risk [57]. The distribution of recurrence scores in MBC cases was similar to that in 2455 contemporary FBC cases. These results suggest that Oncotype Dx™ may have an important role to play in bringing precision into the management of selected MBC cases.

BRCA2 Mutations

Kwiatkowska et al. set out to determine whether MBC cases with a germline mutation of *BRCA2* had a worse or better prognosis than those with sporadic disease [58]. The study group included 43 MBC cases of whom 12 (28%) had *BRCA2* mutations. ER, PR and AR status was determined by IHC. Men with *BRCA2* mutations had earlier mean age at diagnosis (54.4 versus 62.3 years) but carriers and non-carriers did not differ in terms of tumour size, nodal status, grade and receptor status. There was a significant worsening of 5-year overall survival in *BRCA2* carriers (25% versus 86%). Additionally patients with AR+ve tumours had significantly worse 5 year OS (71% versus 57%).

Johansson et al. analysed 56 fresh frozen MBC specimens using high-resolution tiling bacterial artificial chromosome (BAC) arrays [59]. What emerged was a broad pattern of aberrations, confirming the heterogeneity of MBC. Genomic gains occurred more frequently in MBC compared with FBC. Gains were often whole chromosome arms but loss of DNA was less frequent than that seen in FBC. They identified two genomic subgroups among MBCs; male-complex and male-simple. The former was similar to the previously luminal-complex FBC subgroup, but the latter appeared to be a new subgroup of MBC, not seen in FBC. It was proposed that MBC can be separated into subgroups with differing prognoses with male-simple being confined to men.

After this discovery the same group analysed 66 fresh frozen MBC specimens with Illumina Human HT-12 bead arrays as a discovery set and used tissue microarrays from 220 MBC as a validation set [60]. MBC tumours were classified into two subgroups, luminal M1 and luminal M2 and these were recapitulated in the external MBC dataset. Luminal M2 cancers had high expression of immune response genes and ER-associated signalling genes. Although luminal M1 tumours were ER positive on IHC there were fewer genes ER associated signalling genes with a more aggressive behaviour and a worse prognosis. After analysis of two of the most differentially expressed genes, class 1 human leukocyte antigen (HLA) and N-acetyltransferase-1 (*NAT1*), it emerged that there was a significantly better survival in MBC overexpressing both. Furthermore in a multivariate analysis, *NAT1* remained as a significant prognostic marker.

In the Italian Multicenter Study on MBC 382 cases were subjected to genetic testing and 50 were found to be *BRCA* carriers [47]. *BRCA2* mutations were associated with high grade tumours which were more likely to be PR-ve and HER2+ve. Using IHC, 4 molecular subtypes of were identified with the commonest being luminal A (68%). Luminal B comprised 27% of MBC and only 2% were HER2 +ve and 4% triple negative. There was a strong association between *BRCA2* mutations and luminal B and HER2 positive phenotypes.

Further supportive data was reported by the Department of Oncology at University Federico II of Naples where between 1989 and 2014, 47 cases of MBC were seen [50]. There were 42 (88%) men with ER+ve tumours and 38 (81%) that were PR+ve. In this series 13 (27%) had HER2+ve tumours and 3 (7%) were triple negative. *BRCA* status was known for 17 patients and there was 1 man with a *BRCA1* mutation and 5 *BRCA2* carriers. Patients with a *BRCA1/2* mutations had a significantly worse estimated 10-year survival (50% versus 100%).

Hypoxia

Tan et al. examined tissue microarrays from 456 FBC specimens having stained for hypoxia-inducible factor (HIF)-1a, prolyl hydroxylase PHD1, PHD2, PHD3, factor inhibiting HIF (FIH)-1, and carbonic anhydrase IX (CA IX) [61]. Additionally

subtypes were determined by IHC so that hypoxic markers of each phenotype could be established. Basal phenotype comprised 14% of the cancers and of these 28% were carbonic anhydrase IX positive compared with only 5% of the luminal cancers. There was a significant reduction in disease-free survival of patients with basal cancers with the majority expressing one of the PHD enzymes together with FIH-1. CAIX expression was associated with resistance to chemotherapy suggesting that a possible new approach would be to target the HIF pathway.

To determine whether these intriguing findings were applicable to MBC, Kornegoor et al. performed IHC on 134 specimens looking for extent of fibrotic foci together with expression of HIF-Ia, CA IX and glucose transporter 1 (Glut-1) [62]. Fibrotic foci were present in one quarter of the MBC specimens and these were significantly associated overexpression of HIF-1a. Five year overall survival was significantly worse in patients with fibrotic foci >8 mm (47% versus 70%) and also in those overexpressing HIF-1a (50% versus 78%). Carbonic anhydrase IX expression however was unrelated to pathology or prognosis. On multivariate analysis HIF-1a overexpression was the major predictor of survival.

Deb et al. measured HIF1A and CAIX expression in a large series of 286 MBC cases to examine the significance of hypoxic [63]. Of these, 61 had familial disease *BRCA2* (28), *BRCAX* (30) and *BRCA1* (3) with 225 suffering from sporadic MBC. Overall 31% of MBC expressed either HIF1A or CAIX with the former predominating (P = 0.004) in sporadic cases and an increased tumor size (P = 0.003). Expression of HIF1A was associated with worse 10-year DFS in sporadic MBC (35% versus 87%). In contrast CAIX positivity worsened 10-year survival in familial MBC (33% versus 63%). The authors suggested that the reduced frequency of hypoxic drive in MBC might arise from possibly from the different breast microenvironment in males with prognostic impact of HIF1A positivity exerting a deleterious role only in sporadic disease because of other more dominant mitogens in familial disease.

GATA-3

GATA-3 is a transcription factor which plays a central role in human growth and differentiation. It is highly expressed in luminal A subtype of breast cancer and GATA-3 levels are an independent prognostic marker, with recurrence being more frequent in tumours with low expression [64]. Multivariate analysis however indicated that GATA-3 was not an independent prognostic marker.

Gonzalez assessed GATA-3 by IHC in 19 MBC and 164 FBC treated at Emory University School of Medicine and reported that GATA-3 positivity was present in 6 (32%) MBC and 135 (82%) FBC [65]. In FBC, 82% of GATA-3+ve cancers were grade I/II and 76% of GATA-3-ve carcinomas were grade III whereas no significant correlation was seen in men. There was a significantly increased mortality in GATA-3-ve FBC but no effect of GATA-3 status in MBC.

Plasminogen Activator

The capacity of cancer cells to invade the extracellular matrix (ECM) is dependent upon multiple enzymes including the serine proteases, one key group of which are the plasminogen activators (PA). These degrade ECM by converting plasminogen to plasmin. There are 2 types of PA, urokinase type plasminogen activator (uPA) and tissue type plasminogen activator (tPA). The former attaches to the cell membrane after binding with a receptor (uPAR) and this can be inhibited by plasminogen activator inhibitor 1 (PAI-1). In FBC elevated levels of uPA, uPAR, and PAI-1 are associated with a poorer prognosis whereas there is an improvement in outcome for those with increased tPA.

Moredo Anelli et al. examined 32 MBC specimens using IHC to identify uPA, uPAR, PAI-1, and tPA [66]. PAI-1 was found in the cytoplasm of 14 (44%) of the cases. Within the cytoplasm of fibroblasts uPA was present in 90%, uPAR in 62% and PAI-1 in 56%. In macrophage-like cells the respective staining rates were 75%, 53% and 31%. There was no significant expression of stromal tPA and these findings were similar to those in FBC.

Meijer-van Gelder conducted a case-control study with specimens from 40 MBC and 180 matched FBC together with 4114 historic FBC cases [67]. They measured ER, PR, cathepsin D, pS2-protein, together with uPA, uPAR, PAI-1 and PAI-2. Whereas PR levels were higher in males those of uPA, PAI-1, PAI-2 and cathepsin D were lower. In multivariate analysis of the 8 potential prognostic variables PAI-1 was the sole independent predictor of poor prognosis in MBC. This being so it is strange that there have been no further publications on PA and MBC prognosis since 2001.

Hippo

The Hippo pathway is an essential part of embryonic development and alterations can lead to the emergence of an oncogenic state with accelerated cell growth, reduced apoptosis, modification of stem cell function and malignancy. This overgrowth was said to be hippopotamus-like. Deregulation of Hippo has been shown to promote FBC. Pinto et al. examined the micro RNA (miRNA) profile in 24 MBC and 43 FBC [68]. Using pathway enrichment analysis they found that there was upregulation of 157 pathways in MBC and 128 in FBC. Having previously shown frequent down-regulation of RAS association domain family protein 1 isoform A (RASSF1A) in FBC, they concentrated on the MAPK and the Hippo signalling pathways, both regulated by RASSF1A. They found significant upregulation of miR-152 and miR-497 in MBC together with down-regulation of RASSF1A and NORE1A interacting gene. This suggested an indirect interaction between miRNAs

and the two genes and was the first evidence of different microRNA expression patterns in MBC and FBC.

De Bernadetto et al. carried out IHC on tumour tissue microarrays from 129 MBC cases, looking for expression of Hippo transducers TAZ/YAP, together with their target CTGF [69]. Tumours were deemed positive for TAZ/YAP-driven gene transcription if there was co-expression of TAZ, or YAP, and CTGF. Patients with TAZ/CTGF and YAP/CTGF positive tumours had reduced overall survival compared with negative cases. On multivariate analysis TAZ/CTGF and YAP/CTGF expression were independent prognostic variables.

3-Hydroxy-3-methylglutharyl-coenzyme A reductase (HMG-CoAR) catalyses the rate-limiting step in the mevalonate pathway involved in steroid hormone synthesis. Because of this, the same group analysed 124 MBC samples to examine the relationship between HMG-CoAR and endocrine receptors (ER, PgR, together with AR). There was a positive association between Hippo transducers receptor expression. Furthermore MBC cases whose tumours were HMG-CoAR positive had significantly better 10-year OS (64% versus 51%). After excluding tumours of unusual histology, the protective effect of HMG-CoAR was confirmed.

Eukaryotic Initiation Factor 4E (elf4E)

High activity of eukaryotic initiation factor 4E (eIF4E) has been shown to be associated with poor prognosis in FBC. Deregulation occurs if the binding protein 4E–BP1 is phosphorylated. Millican-Slater et al. used IHC to examine expression levels of eIF4E, 4E–BP1, 4E–BP2 and phosphorylated 4E–BP1 (p4E–BP1) in a group of 337 MBC [70]. They found that eIF4E expression had no effect on prognosis. Despite this p4E–BP1 expression was associated with significantly worse DFS l at 10 years (negative 75% positive 34%). The authors' interpretation was that p4E–BP1 was a surrogate biomarker for a functionally active upstream kinase.

Prognostic Models

A variety of prognostic models have been developed for FBC: the Morphometric Prognostic Index (MPI), Nottingham Prognostic Index (NPI), Adjuvant! Online and Predict. Van der Pol et al. investigated the applicability of these models to outcome in 166 MBC cases [71]. Each model was able to define groups with good, moderate and poor survival with highly significant P-values. The performance of all four models was similar except that Predict tended to overestimate survival in MBC. At least in this respect there is overlap of behaviour of male and female breast cancer.

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Chapter 12
Future Directions

Abstract A rare disease can be a source of worry for both the patient and the doctor. There is one approach which will improve the treatment of male breast cancer and convince the patient that he is being managed optimally and that is to set up collaborative clinical and research networks based around a few hubs. At present, prevention is not a feasible option but health education has an important role in dispelling ignorance and encouraging early presentation of those with potential symptoms or signs of male breast cancer. Structured investigation should enable the majority to be reassured while the few with cancer can be promptly diagnosed and, when possible, specimens obtained not only for routine pathology but also for research tissue banks. There needs to be a greater emphasis on neoadjuvant treatment, mostly endocrine in nature to shrink primary tumours and enable more men to have less mutilating surgery. In the past many attempts were made to establish the similarities between male and female breast cancer. Sophisticated molecular analyses are now identifying multiple striking differences and the exploitation of these will in time lead to better prognostic models and new tailored therapies for male breast cancer.

I like the dreams of the future better than the history of the past. Thomas Jefferson

Collaboration

Confronted with a diagnosis of breast cancer a man may experience a miscellany of emotions: fear, anger, depression and guilt. Transfixing these problems is the question "Why me?" To deal effectively, sympathetically and knowledgably requires medical and nursing personnel who have experience with this rare disease. This is difficult to achieve in local hospitals so the best approach will be to set up national networks based around hubs of expertise. In the UK, with 350 new cases of MBC every year, 3 hubs would each oversee >100 cases annually.

It would not be necessary for patients to travel to the hub. Their cases would be discussed by the central multidisciplinary meeting together with a senior clinician

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from the referring hospital. The information needs of newly diagnosed cases could be met by an outreach services provided by appropriately trained Breast Care Nurses with support from selected MBC patients, either at home or in the local hospital. A major step towards reassuring worried patients would be the knowledge that they were being cared for by experienced professionals. Modern technology facilitates this without the need to travel.

The hub team would ensure central registration of all MBC together with a minimum data set so that epidemiological studies could be rendered more effective. As an example, there is evidence that statins may reduce the risk of recurrence in women with breast cancer [1, 2] and reduce mortality [3]. This needs examination in patients with MBC since there is an increasing drive to prescribe statins almost ubiquitously.

Once a treatment plan had been formulated and agreed both centrally and locally, the patient's suitability for participation in randomised controlled trials should be considered. Additionally a central library of tissue and blood specimens would enable many pressing questions to be answered. This should be the first step in a serious approach to improving our understanding of MBC. To paraphrase a once popular British Prime Minister the answer is "Collaboration, collaboration, collaboration". We have a potentially valuable resource of MBC which is at present underexploited. As an example of what can be achieved, geneticists have been at the forefront of collaboration in the investigation of MBC, yielding important data which indicate some of the differences between the disease in males and females. Another instance of very successful clinical research collaboration is the Danish Breast Cancer Cooperative Group (DBCG) which has carried out landmark randomised trials in a country with only 5½ million inhabitants [4]. In England and Wales, a large national case–control study is underway to investigate potential risk factors and genetics for breast cancer in men compared with their non-blood relatives as controls. Participants were accrued between 2007 and 2016 (REC reference 07/MRE01/1).

Education

At the forefront of the problem is the stereotypical male psyche which seeks out and enjoys high-risk activities. This is not just a problem of downhill off piste skiing or sky-diving but there has been a hard-core of macho magnetism that draws men to smoke legally and illegally, overdrink and under-exercise. This is associated with a general feeling of invulnerability leading to avoidance of simple health precautions including contact with doctors [5]. In the Western world we are in the midst of an epidemic of obesity which on a systemic basis will increase the risk of malignancy including MBC. At a local anatomical level the incidence of gynaecomastia is increasing and this will delay diagnosis because the patient will not be aware of the cancer until it has emerged from the subcutaneous adipose blanket.

Health awareness cannot be forced upon men but the peer-group attitudes may be modified by sensitive health education in secondary schools. This may be of particular importance in sub-Saharan Africa where MBC represents ≥10% of all cases [6] . The possible explanation is immune deficiency from endemic hepatitis B which affects one in eight of the inhabitants [7].

Educational drives are likely to focus on reducing the population risks of obesity including maturity onset diabetes and cardiovascular disease together with encouragement not to start smoking. As a result education about rare diseases such as MBC is likely to be engulfed by the tsunami of information concerning more pressing and common problems. In any discussion of breast cancer it should be pointed out that males can be affected and the commonest symptom is a lump. Although approximately 80% of MBC patients present with a lump nevertheless as with FBC pain may be present in 10% of cases. As part of the counselling of *BRCA* mutation carriers the potential risk for male siblings should be discussed to target this high risk group [8].

Diagnosis

Triple assessment should be standard in a man with a suspicious breast mass but can be omitted in asymptomatic individuals with gynaecomastia. In terms of resource allocation this will become a larger problem as more men develop pseudogynaecomastia as a result of the obesity epidemic. All MBC cases should have bilateral mammography with breast and axillary ultrasound to determine the extent of the malignancy. Core biopsy represents the standard of care for work-up of MBC since knowledge of receptor status and tumour grade are essential for optimal management [9]. This will enable the collection of a minimum dataset for all cases of MBC. Such an approach is essential for the planning and analysis of the large multicentre trials which it is hoped will affect a sea change in our understanding of MBC.

Studies from the US have clearly shown that socio-demographic differences are central to the worse outcome of poorer people so that to a major extent the solution may be political [10]. In the sum of human problems, MBC does not feature as an important concern but educational and economic improvements will lead to a greater likelihood of general health awareness. Seeking medical help with early symptoms that could herald malignant disease, including MBC, will enable earlier diagnosis with need for less extensive local and systemic therapy with a greater chance of long-term cure.

Risk Factors

There is an inherent paradox which needs investigation. Genotypic males who take estrogens, often a part of management of their transsexuality, are at increased risk of breast cancer but approximately half of the tumours that develop are estrogen

receptor negative [11, 12] . This suggests that there is an alternative pathway to the usual model of estrogen stimulation of estrogen sensitive tissue. Studies of hormone replacement therapy in females have demonstrated that the combination of estrogen and progestin increases FBC risk compared with estrogen alone [13]. Endocrine interventions require structured investigation in those centres specialising in gender realignment for transsexual individuals.

Another paradox concerns the lack of association between alcohol intake and incidence of MBC [14] whereas there is a clear relationship between daily intake and risk of FBC [15]. This is all the more surprising in that obesity is a significant side effect of increased alcohol intake and is also a major risk factor for MBC. Government interventions to reduce obesity have not so far met with great success. It is to be hoped that the impact of obesity on cancer risk will be understood eventually by the general public. If this happens they may then respond by behavioural change in a similar manner to the tobacco/lung cancer studies by giving up smoking. Self-interest is likely to be the major driver towards a more healthy lifestyle.

Vive la Difference

Very considerable effort has been expended to show that after matching for stage there is little difference in the outcome for women and men with breast cancer. Worthy though this toil may have been, it misses the more important point of the emerging differences between MBC and FBC. These are not congruent diseases and some of the asymmetric features are outlined in Table 12.1. Although mutations of *BRCA1* are responsible for approximately 7% of FBC they are associated with only 1% of MBC. Conversely *BRCA2* mutations are associated with 1 in 10 of MBC cases versus only 1 in 50 of FBC.

Table 12.1 Asymmetric features of MBC and FBC

Feature		MBC	FBC
Genetics	*BRCA1* + ve *BRCA2* + ve	1% 10%	7% 2%
SNPs and risk		2/12 risk↑ 1/12 risk↓	12 risk↑
Luminal A Luminal B HER2 Basal		84% 12% 0% 0%	48% 25% 18% 9%
Cell cycle kinase inhibitors $P27^{kip1}$ $P21^{Waf1}$		96% 70%	44% 32%
Eukaryotic initiation factor 4E (eIF4E)		No effect on prognosis	Worse prognosis
GATA3		No effect on prognosis	Worse prognosis
(Topo II-a) (CEP17) duplication		No effect on prognosis No effect on prognosis	Worse prognosis Worse prognosis

In a large genome-wide association study, with 433 MBC cases and 1569 male controls Orr et al. examined whether the 12 SNPs that had been shown to be associated with increased risk of FBC were also involved with MBC [16]. Their findings were surprising. Only 5 of the 12 SNPs were significantly associated with MBC: rs13387042, rs10941679, rs9383938, rs2981579 and rs3803662. When the odds ratios for MBC and FBC were compared only 3 SNPs showed significant differences between the genders and these were rs13387042, rs3803662, and rs6504950 and for the latter the risk was reduced in males.

There are substantial differences in the molecular profile of MBC and FBC cases, the predominant male subtype is luminal A (84%) compared with 48% of FBC. Both HER2 and basal types comprise a very small proportion of MBC. Andres et al. showed over-expression of several genes including *NAT1* (gene product N-acetyltransferase 1) and *TBC1D9* (encoding TBC1 domain family member 9) in MBC compared with FBC [17] . These are possibly related to ER and both are potential therapeutic targets. Conversely there are several genes, *GATA3* [18], *Topo IIa* and *CEP1* whose overexpression is associated with a worse prognosis in FBC but which appear to have no prognostic significance in MBC [19] . The cell cycle kinase inhibitors $P27^{kip1}$ and $P21^{Waf1}$ are more frequently found in MBC and may serve as indicators of endocrine response [20]. Although elevated levels of eukaryotic initiation factor 4E (eIF4E) are associated with poor prognosis in FBC, eIF4E has no direct impact in MBC outcome [21].

Neoadjuvant Treatment

Neoadjuvant treatment not only provides an approach to tumour shrinkage but can also be used as a window of opportunity to test the biological impact on the tumour of new therapies. As a disease which is usually due to ER + ve tumours which is often stage II/III at diagnosis, endocrine neoadjuvant therapy would seem to be an obvious approach but which has been underemployed. Given that tamoxifen is superior to aromatase inhibitors as adjuvant therapy in MBC because the latter do not inhibit testicular estrogen synthesis [22], neoadjuvant trials should concentrate on improving the results of tamoxifen alone.

Comparisons need to be conducted with additional gnRH analogues such as goserelin and buserelin or the combination of these with AIs. Such studies need to be conducted within a framework of close monitoring of side effects and acceptability of these, possibly for 6 months to a male cohort. For those responding treatment might be extended under trial conditions to 12 months. With pre-defined criteria, for those achieving a complete response the role of breast irradiation alone could be examined.

If there is a partial response with no nipple involvement this would provide an opportunity to compare nipple-preserving mastectomy with total mastectomy followed by radiotherapy, both in terms of patient acceptability and local control. None of these trials are possible at present because of the *ad hoc* nature of MBC

management in scattered centres without an overarching agreement to conduct multicentre randomised controlled trials. Postmastectomy radiotherapy has been shown to improve local control and survival in selected FBC cases but as yet there is no convincing evidence of efficacy in MBC [23].

Tamoxifen has been tested in FBC prevention trials and shown to reduce the incidence of ER + ve tumours by approximately 50%. Since the majority of MBC is ER + ve the potential benefits could be substantially better provided that a sufficiently high risk group of males could be identified. As a start, *BRCA2* carriers would be a potential target and are likely to be more motivated to participate because of their likely experience of the impact of breast cancer on their affected relatives.

Trying to obtain a clear picture of MBC has so far proved elusive. It is like putting together pieces of a mosaic with missing components. We will continue to struggle and our patients will suffer unless there is general agreement to collaborate. The molecular tools are at hand but what we need is agreement to set up the long overdue international randomised clinical trials and marry the cellular data to the results of structured treatment with adequately powered patient participation.

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