REVIEW

The endocrinology of male breast cancer

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Abstract

Male breast cancer (MBC) is a rare disease but, as a result of epidemiological collaborations, there is now greater clarity concerning endocrine risk factors. The significant rise in global age-standardised mean BMI in men is likely to lead to increases in incidence of maturity-onset diabetes and MBC. The metabolic changes accompanying obesity decrease androgens and sex hormone-binding globulin (SHBG), thereby increasing available oestrogens. The higher rates of MBC in North and Equatorial Africa are largely due to liver damage from endemic bilharziasis and hepatitis B causing elevated oestradiol (E_2) levels from hepatic conversion of androgen. Klinefelter's syndrome (XXY) is associated with a 50-fold increase in incidence of MBC compared with XY males, and this is the most pronounced evidence for testicular malfunction amplifying risk. Delay in presentation means that up to 40% of cases have stage III or stage IV disease at diagnosis. No randomised controlled trials have been reported on endocrine treatment of advanced disease or adjuvant/neoadjuvant therapy following or preceding surgery. Tamoxifen is the most effective endocrine therapy, but side effects can lead to non-compliance in a substantial number of men. Aromatase inhibitors are less effective because they do not inhibit testicular oestrogen production. There is an urgent need for collaborative trials to provide an evidence base for the most effective endocrine and least toxic therapies for men with breast cancer.

Key Words

- ▶ male breast cancer
- ▶ risk factors
- ▶ obesity
- ▶ Klinefelter's
- ▶ endocrine therapy

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Introduction

The rarity of male breast cancer (MBC) has severely impeded the investigation of this disease so that compared with female breast cancer (FBC), our knowledge is rudimentary. There is however some evidence that the incidence is increasing. According to Surveillance, Epidemiology and End-Results (SEER) data, in the United States, there was a significant rise from 0.86 to 1.08/100,000 male population between 1973 and 1998 (Giordano *et al.* 2004). At a molecular level, there are important gender differences, 95% of MBC being luminal A or B (Ge *et al.* 2009, Shaaban *et al.* 2012), compared with 73% of FBC (Sorlie *et al.* 2003). Both basal and HER2 phenotypes are rare in men. In terms of genetics, approximately 10% of MBC cases have *BRCA2*

mutations and <1% are associated with *BRCA1* mutations. *BRCA2* mutations are found in 4–40% of familial MBC, compared with 5–10% of hereditary FBCs (Sousa *et al.* 2013).

Since 95% of MBC are oestrogen receptor positive (ER+ve), this implies a major endocrine role in both development of MBC and treatment of the disease.

There is another important facet, namely those male attitudes that dismiss symptoms and eschew contacts with doctors (Pill *et al.* 1988). Because few men exhibit any breast awareness, there is often a significant delay in the diagnosis of MBC. As a result, up to 40% of MBC are stage III or stage IV at the time of diagnosis so that, for the

majority, endocrine therapy forms a major constituent of their first-line systemic treatment (Fentiman *et al.* 2006).

Endocrine risk factors

The occurrence in men of a predominantly female cancer led to the suspicion that these individuals would exhibit an altered endocrine milieu with either too little androgen or too much oestrogen. Investigations have revealed that this is true for some cases of MBC. Casagrande *et al.* conducted a case-control study comprising 75 MBC cases and 75 age-matched neighbourhood controls to examine various potential endocrine risk factors (Casagrande *et al.* 1988). Clinical variables included history of fertility, marital status, weight, alcohol, tobacco and drugs potentially causing gynaecomastia. Additionally, family history of breast cancer was sought together with past radiation exposure. The laboratory analyses included sex chromatin, together with assays for serum levels of prolactin, testosterone, oestrone (E_1), oestradiol (E_2) and sex hormone-binding globulin (SHBG). E_1 , E_2 and oestriol (E_3) concentrations were measured in urine. Of all the variables examined, only obesity proved to be a risk factor. Those weighing ≥ 80 kg at age 30 years had a doubling of risk compared with those < 60 kg at age 30 years. SHBG levels were inversely related to weight suggesting that there was a greater availability of free oestrogen in the obese.

Since then, several large studies have confirmed the association between BMI (weight/height²) and risk of MBC (Hsing *et al.* 1998, Ewertz *et al.* 2001, Brinton *et al.* 2008, 2010). The results relating to BMI at the time of diagnosis are summarised in Table 1. These show a clear dose-response rate increasing BMI and MBC risk. Using a different approach, Keinan-Boker *et al.* examined the impact of adolescent BMI on subsequent risk of MBC (Keinan-Boker *et al.* 2018). They amassed a cohort of 1,382,093 Israeli males aged between 16 and 19 years of age. After follow-up of 29,386,233 person-years, 100 had been diagnosed with MBC and the variables derived from 97 were entered into a multivariate analysis. Compared with individuals having a BMI of 18.5–24.9 kg/m², those with an adolescent BMI of 25.0 to < 30.0 kg/m² had a doubling of risk hazard ratio (HR)=2.01. The obese individuals with a BMI of ≥ 30.0 kg/m² had an almost 5-fold increase in risk (HR=4.97).

This has major implications for the future since there is a pandemic of obesity which shows no signs of abating. The Non-Communicable Disease (NCD) Risk Factor

Table 1 Risk of male breast cancer in relation to BMI.

Author	N	Subsets	RR
Hsing <i>et al.</i> (1998)	178	BMI quartiles	
		1	1.0
		2	1.3
		3	1.6
		4	2.3
Ewertz <i>et al.</i> (2001)	282	BMI tertiles	
		< 25	1.0
		25–30	1.7
Brinton <i>et al.</i> (2008)	121	> 30	2.1
		BMI tertiles	
		< 25	1
Brinton <i>et al.</i> (2010)	2405	25– < 30	1.07
		≥ 30	1.79
		BMI tertiles	
		< 24.6	1
		24.7–27.4	1.15
		> 27.4	1.3

Collaboration has reported trends in mean population distribution of mean BMI, using 1698 population databases comprising sources, with more than 19.2 million adults (9.9 million males and 9.3 million females (NCD Risk Factor Collaboration 2016). Between 1975 and 2014, global age-standardised mean BMI in men increased from 21.7 kg/m² to 24.2 kg/m². During these 40 years, age-standardised obesity prevalence in males more than tripled from 3.2% to 10.8%.

Endocrine changes in obesity

Ewertz *et al.* conducted a Scandinavian case-control study with 156 MBC and 468 controls matched for country and age (Ewertz *et al.* 2001). They reported increased risk for those with a family history of breast cancer (odds ratio (OR)=3.3) obesity 10 years before diagnosis (OR=2.1) and diabetes (OR=2.6). Bekaert *et al.* examined androgen metabolism in 57 men with morbid obesity of whom 33 had type 2 diabetes compared with 25 men of normal weight (Bekaert *et al.* 2015). Blood levels of total and free testosterone levels were reduced in the obese males and further decreased in those with diabetes. Expression of aromatase was similar in both groups, and androgen levels were unrelated to aromatase expression. There was an inverse relation between subcutaneous adipose tissue (SAT) cell size and free testosterone suggesting that it was SAT cell size and not SAT aromatase expression, which triggered decreased testosterone in the obese.

Whiteman *et al.* investigated whether intrauterine exposure to high levels of oestrogen might increase the risk of MBC in a cohort study of 115,235 male twins

(Whiteman *et al.* 2000). After >3.5 million person-years of follow-up, they reported 11 cases of MBC, whereas there were 16 expected cases suggesting that *in utero* maternal oestrogens do not lead to a significant increase in foetal risk of MBC.

In another twin study, Vihma *et al.* examined the relationship between weight and serum sex hormone levels in fat from young Israeli adult male monozygotic twin pairs of average age 32 years (Vihma *et al.* 2017). Of the 18 pairs, there were 9 discordant for BMI with a difference of $\geq 3 \text{ kg/m}^2$. In discordant pairs, serum dihydrotestosterone (DHT) was lower and mRNA expressions of both DHT-inactivating AKR1C2 ($P=0.021$) and cortisol-producing HSD11B1 were higher in the heavier of the two twins. Additionally, the heavier twins had higher free E_2 . Irrespective of age, there was an inverse relation between the extent of subcutaneous fat and both total and free DHT. There was a positive correlation between fat and SHBG levels with reduced concentrations of DHT resulting from increased degradation by AKR1C2 and HSD11B1.

Medical conditions and MBC risk

Brinton *et al.* accessed 26 million hospital discharge records from the US Veterans Administration between 1969 and 1996 to identify those medical conditions, which were associated with an increase in risk of subsequent MBC (Brinton *et al.* 2010). Of the 4,501,578 males in the cohort, 642 were diagnosed with MBC. Table 2 gives the results, indicating that gynaecomastia and Klinefelter's syndrome (KS) were associated with the highest relative risks (RRs). The link with diabetes disappeared after adjustment for obesity, but that for gynaecomastia persisted. This latter finding is difficult to evaluate since recorded cases will have been a mixture of true and pseudo gynaecomastia.

Klinefelter's syndrome

In 1942, Klinefelter *et al.* reported a syndrome comprising gynaecomastia, testicular dysgenesis and sterility (Klinefelter *et al.* 1942). Subsequently, it was shown that this was the result of an extra X chromosome (XXY) (Jacobs & Strong 1959), which affects 2/1000 of new born boys with up to 50% remaining undiagnosed (Bojesen *et al.* 2003, Herlihy *et al.* 2011). In KS, plasma total and free testosterone levels are low with elevation of E_2 , luteinising hormone (LH) and follicle-stimulating hormone (FSH) (Wang *et al.* 1975). Additionally, there is

Table 2 Pre-existing medical conditions and risk of MBC (Brinton 2010).

Condition	RR (95% CI)
Diabetes	1.30 (1.05–1.60)
Obesity	1.98 (1.55–2.54)
Orchitis/epididymitis	1.84 (1.10–3.08)
Klinefelter's syndrome	29.64 (12.26–71.68)
Gynaecomastia	5.86 (3.74–9.17)

increased peripheral conversion of testosterone to E_2 . E_2 synthesis is normal, but there is dampening of the normal fluctuations in LH, FSH, testosterone and E_2 .

In a series of 150 British MBC cases, 5 (3.3%) proved to be chromatin positive (Harnden *et al.* 1971) and of 93 Swedish MBC patients, there was a 7.5% prevalence rate of KS (Hultborn *et al.* 1997). This translated into a 50-fold increased risk in KS compared with XY males but interestingly, the median age at diagnosis was 72 years in both groups, suggesting that KS does not accelerate the development of MBC. To determine the incidence of malignancy in KS, Swerdlow *et al.* investigated a cohort of 3518 men with cytogenetic confirmation of the diagnosis (Swerdlow *et al.* 2001). In comparison with the general population, those with KS were more likely to die of lung cancer (standardised mortality rate (SMR), 1.5) and breast cancer (SMR, 57.8), but there was a much lower rate of prostate cancer deaths (SMR 0).

Diabetes

Dhindsa *et al.* measured plasma E_2 , testosterone, LH, FSH and SHBG in 240 men with type 2 diabetes and found that free E_2 in those with reduced free testosterone was lower than that in men with normal free testosterone concentrations (Dhindsa *et al.* 2011). Free E_2 was directly related to free testosterone but unrelated to BMI or age indicating that suppression of the hypothalamo–hypophyseal–testicular axis in men with subnormal free testosterone and type 2 diabetes did not lead to elevated E_2 concentrations. Arthur *et al.* examined the endocrinology of men with impaired fasting glucose and/or impaired glucose tolerance (pre-diabetes) (Arthur *et al.* 2017). The subjects were derived from 1139 men aged >20 years who had taken part in the Third National Health and Nutrition Examination Survey. After adjustment for age and ethnicity, geometric mean total serum testosterone concentration and SHBG levels were significantly lower in the pre-diabetics. Additionally, the pre-diabetic men had higher free E_2 levels in serum.

Hepatic damage

There are substantial geographical variations in the incidence of MBC with the highest rates observed in North and Equatorial Africa probably due to liver damage. A study from Alexandria reported that 6.8% of breast cancer cases were male (El-Gazayerli & Abdel-Aziz 1963). It is likely that the major cause was endemic bilharziasis (schistosomiasis), which was identified in 7/8 of the tested MBC cases. A similarly large proportion of MBC was reported from Sudan and Ethiopia where almost 14% of breast cancer cases were male (Awadelkarim *et al.* 2007, Gebremedhin & Shamebo 1998).

After dermal entry *Schistosoma mansoni* or *S. haematobium* targets the liver, surviving on a diet of erythrocytes, reaching up to 1 cm in length. It elicits a granulomatous immune response causing irreversible fibrosis (cirrhosis). In cirrhosis, there is significantly increased conversion of androstenedione (A) to E_1 , E_2 and testosterone (Gordon *et al.* 1975). Testosterone is in turn converted to E_1 and A, resulting in the elevation of plasma A and E_2 with decreased plasma testosterone. Levels of A in these men are similar to those found in normal females. Metabolic clearance rate of A is unaltered, whereas testosterone clearance is decreased. Elevated E_2 levels in cirrhosis are mostly due to hepatic conversion from the androgens.

Another major source of liver damage in Sub-Saharan Africa is hepatitis B where the highest male/female incidence ratio 1:10 for breast cancer has been recorded (Hassan & Mabogunje 1995). Within populations, hepatitis B surface antigen HBsAg has been found in 6.5–25% of tested individuals with the highest rate being found in Zimbabwe (Zampino *et al.* 2015).

Testicular dysfunction

Testicular damage has been shown to be an important risk factor for MBC. In an early case–control study with 53 MBC cases, Schottenfeld *et al.* reported that 3 cases had suffered post-pubertal mumps (Schottenfeld *et al.* 1963). In a larger study of 181 MBC cases and controls selected by random digit dialling, it emerged that 19 cases (11%) had atrophic, enlarged or inflamed testes compared with 22 (12%) of the cancer controls (Keller 1967). Mabuchi's study of 52 MBC cases and 52 controls matched for age and ethnicity reported a significant association of MBC with mumps diagnosed at or after age 20 years (Mabuchi *et al.* 1985). Additionally, 7 cases had worked in hot environments such as steel mills and blast furnaces compared with none

of the controls. Further confirmation of testicular damage from a warm ambient work temperature was found in a Franco-Swiss case–control study where working in a hot environment was reported by 5 (5%) cases and 5 (2%) controls (Lenfant-Pejovic *et al.* 1990). A larger study of 227 MBC cases and 300 age-matched controls found no excess of mumps but undescended testis had occurred in 7 cases and 1 control giving a RR of 11.6 (Thomas *et al.* 1992). More of the cases had had prior inguinal herniorrhaphy, orchidectomy and testicular injury.

Larger collaborations with greater statistical power have helped to clarify the situation. In the study of Brinton *et al.*, 642 MBC cases were amassed from a cohort of >4.5 million males so that adjustment for age, ethnicity and year of diagnosis, could be made (Brinton *et al.* 2010). This confirmed that a prior history of orchitis or epididymitis led to a significant increase in RR of MBC (RR=1.30, 95% CI 1.05–1.60). The Male Breast Cancer Pooling Project was a meta-analysis of data from 11 case–control and 10 cohort studies and yielded different results (Brinton *et al.* 2008). Cryptorchidism and orchitis elevated the OR, without statistical significance, but for those who had never fathered children, risk was significantly increased (OR=1.29; 95% CI=1.01–1.66). The results are summarised in Table 3. Despite variations in the findings, testicular damage emerges as a risk factor for MBC. This raises the intriguing possibility that testosterone replacement for these men might not only improve quality of life and reduce mortality from cardiovascular disease (Hwang & Miner 2015) but also potentially reduce the risk of MBC.

Endocrine treatment

Because of delayed presentation of MBC endocrine treatment was used originally to manage advanced or metastatic disease. Since these patients were seen by surgeons, intervention tended to be operative and ablative rather than additive. When Beatson had reported remission of advanced FBC after bilateral oophorectomy, it was an apparently logical step to treat MBC by orchidectomy (Beatson 1896). Although this was capable of effectively palliating pain from bone metastases, it was an unacceptable option for many men. Treves summed up the problem 'The acquiescence to orchietomy seems to us to be a triumph of medical persuasion' (Treves 1949). In a series of 14 men who were offered orchidectomy, this was refused by 8 (57%) (Bezwodna *et al.* 1987).

Again, following publication of other surgical ablations developed for stage III/IV FBC, bilateral adrenalectomies were performed for advanced MBC without killing the

Table 3 Collaborative studies of testicular damage and MBC risk.

Study	MBC cases	Orchitis	Cryptorchidism	No children
VA Ewertz <i>et al.</i> (2001)	642	RR=1.8 (1.08–3.01)		
MBCPP Brinton <i>et al.</i> (2010)	2405	OR 1.43 (1.02–1.99)	OR 2.18 (0.96–4.94)	OR 1.29 (1.01–1.66)

MBCPP, Male Breast Cancer Pooling Project; OR, Odds ratio; RR, relative risk; VA, Veterans Administration.

patient once cortisone became available. Only two series contained >2 cases and of the 10 cases reported by Patel *et al.*, there was a response in 8 (80%) (Patel *et al.* 1984). As a palliative procedure, hypophysectomy was performed in only 10 recorded MBC cases and a response was seen in only 2 (20%) (Luft & Olivecrona 1955, Scowen 1958, Holleb *et al.* 1968, Cortese & Cornell 1971, Kennedy & Kiang 1976). Hypophysectomy was associated with serious complications including diabetes insipidus, cerebrospinal fluid leakage, haemorrhage and meningitis.

The earliest form of additive endocrine therapy was oestrogen, and Treves treated 13 advanced MBC cases but without great success, reporting a response in only 2 cases given ethinylestradiol (Treves 1949) (Table 4). In Donegan's series of 28 MBC cases, 3/5 of those given oestrogens achieved a response (Donegan & Perez-Mesa 1973). The largest cohort was reported by Ribeiro who used diethylstilboestrol and, of the 55 assessable cases, 14 had an objective response and 7 a partial response giving an overall response rate of 38% (Ribeiro 1976). Stilboestrol administration invariably led to gynaecomastia and fluid retention with some men developing thromboembolism and cardiac failure. The emergence of tamoxifen signalled the end of oestrogen therapy for MBC.

Tamoxifen

Tamoxifen was a serendipitous advance in the endocrine treatment of both FBC and MBC. It was originally synthesised as a potential oral contraceptive but was rejected once it became apparent that it stimulated rather than inhibited ovulation (Jordan 2006). Ignominious disappearance was averted by the discovery that it inhibited the uptake of $^3\text{H-E}_2$ by the rat uterus making it an apparent anti-oestrogen. Tamoxifen is a selective oestrogen receptor modulator, which is effective in breast cancer because it blocks α -ER in breast tissue.

From Guy's Hospital, Cantwell *et al.* were the first to report a beneficial effect in metastatic MBC (mMBC) with all 3 patients gaining responses lasting for >6 months (Cantwell *et al.* 1978). Subsequent studies with >10 mMBC cases are summarised in Table 5. In a multicentre study of 31 mMBC cases treated with various dosages of

tamoxifen, complete or partial response occurred in 15 (48%) (Patterson *et al.* 1980). Ribeiro (1983) reported a series of 24 mMBC cases in which tamoxifen achieved a complete response in 5 and a partial response in 4. Bezwoda treated 12 cases of whom 58% responded and 5 were known to have ER+ve tumours (Bezwoda *et al.* 1987).

Adjuvant treatment

As tamoxifen was recognised as an effective and relatively non-toxic treatment for mMBC, it was an obvious candidate for an adjuvant role. To investigate this possibility, Ribeiro and Swindell conducted a non-randomised trial for MBC cases with axillary nodal involvement (Ribeiro & Swindell 1992). Tamoxifen 20mg daily for 2 years was given to a total of 39 MBC cases. Using historical controls matched for stage, the 5-year disease-free survival (DFS) increased from 25% to 56% (Table 6). Side effects (alopecia and skin rash) led to cessation in 2, but the majority of men completed the course of tamoxifen.

Of the 156 MBC cases treated at the MD Anderson Cancer Center between 1944 and 2001, 135 (87%) had non-metastatic disease (Giordano *et al.* 2005). Adjuvant tamoxifen was given to 36 cases of whom 31 (82%) had ER+ve tumours. The 10-year overall survival (OS) was 65% in those given endocrine therapy compared with 45% in the 97 who had no adjuvant endocrine treatment. The large French series included 489 MBC cases of whom 298 had adjuvant, tamoxifen alone (Cutuli *et al.* 2010). Of the 243 cases with pathologically involved axillary nodes, endocrine therapy improved distant DFS from 38% to 72%.

In a Boston series of 42 MBC cases all of whom had ER+ve/PR+ve primary tumours, 21 (50%) received adjuvant tamoxifen (Fogh *et al.* 2010). Overall 10-year

Table 4 Effect of oestrogens on advanced MBC.

Author	N	Agent	Response rate (%)
Treves (1949)	5	Stilboestrol	0
	7	Ethinylestradiol	29
	1	oestradiol	0
Donegan & Perez-Mesa (1973)	5	Stilboestrol	60
Ribeiro (1976)	55	Stilboestrol	38

Table 5 Treatment of advanced MBC with tamoxifen.

Author	N	Response rate (%)	Comment
Cantwell <i>et al.</i> (1978)	3	100	PR 3
Patterson <i>et al.</i> (1980)	31	48	CR/PR 15, SD 5
Ribeiro (1976)	24	37.5	CR5, PR4
Bezuda <i>et al.</i> (1987)	12	58	5 responders ER+ve

CR, complete response; PR, partial response; SD, static disease.

survival was 100% for those having tamoxifen and radiotherapy, 65% in those given tamoxifen alone, 83% for radiation alone and 65% with no adjuvant therapy. In this univariate analysis, adjuvant chemotherapy alone or combined with tamoxifen or radiation had no significant impact on 10-year OS. The authors suggested that this result required validation in a larger study.

In a multicentre study of 50 Korean MBC patients, 42 had known receptor status and 38 (91%) were ER +ve (Hong *et al.* 2016). Use of adjuvant endocrine therapy improved OS in patients with ER+ve tumours (median survival 8.5 years vs 4.2 years for those not given endocrine treatment).

There have been no randomised trials of adjuvant or palliative chemotherapy in MBC. Reported series have been small with variations in regimens and dosage so that no conclusions can be drawn regarding the role of chemotherapy for men with breast cancer.

Problems with compliance

There are gender differences in compliance with tamoxifen therapy so that males are less likely to accept side effects than females. Among 24 MBC cases receiving adjuvant tamoxifen 15 (63%) complained of side effects including reduced libido (29%), weight gain (25%), hot flushes (21%) and mood alterations in 21% (Anelli *et al.* 1994).

Table 6 Results of adjuvant endocrine therapy.

Author	Treated	Survival	Comment
Ribeiro & Swindell (1992)	Tamoxifen 30	5 year DFS 56% vs 25%	Historic controls
Giordano <i>et al.</i> (2005)	Tamoxifen 36	10 year OS 65% vs 45%	Untreated historic controls
Cutuli <i>et al.</i> (2010)	Tamoxifen	Metastasis-free 5 62% vs 24%	Node positive cases
Fogh <i>et al.</i> (2010)	Tamoxifen	10 year OS 100% vs 65%	Tam + RT vs Tam
Hong <i>et al.</i> (2016)	Tamoxifen	Median survival 8.5 vs 4.2 years	Treated vs untreated

As a result of toxicity, 21% stopped tamoxifen within a year of diagnosis, compared with only 10% of females.

At the Ottawa Hospital Cancer Centre, 51 MBC cases received endocrine therapy between 1981 and 2003 (Visram *et al.* 2010). Thirty were given tamoxifen as either adjuvant or palliative treatment, with 50% reporting side effects, in order of frequency, hot flushes, diminished libido, weight gain and general malaise and 24% discontinued treatment, one because of a pulmonary embolism. Similar results were reported from the MD Anderson Cancer Center where 64 MBC patients received adjuvant tamoxifen and 34 (53%) complained of side effects (Pemmaraju *et al.* 2012). These included weight gain in 14 (22%) and sexual dysfunction in 14 (22%) of patients, which led to discontinuation by 13 (20%) with 4 suffering thromboembolism.

Non-compliance costs lives. Xu *et al.* followed a cohort of 116 MBC patients with ER+ve disease and reported that among those advised a 5-year course of tamoxifen, after 1 year, only 75 (65%) were compliant (Xu *et al.* 2012). After 2 years, compliance fell to 46%, and by the final year, only 18% were taking tamoxifen. Significant risk factors for non-compliance included low social support, older age, lack of social support and toxicity. The compliant patients had a 10-year OS of 80% compared with only 50% for the non-compliant MBC cases.

Neoadjuvant endocrine therapy

Considering that 95% of MBC cases have ER+ve tumours, which are often large, it is surprising that no prospective studies of endocrine neoadjuvant therapy have been reported. This means that what could be a useful approach to enable tumour excision rather than mastectomy or to permit less extensive surgery remains untested. The nature of that neoadjuvant endocrine therapy needs to be determined. It has been suggested that the behaviour of MBC is more like postmenopausal than premenopausal FBC (Anderson *et al.* 2004). As a result of randomised controlled trials (RCTs), tamoxifen has been superseded by aromatase inhibitors as first-line adjuvant therapy in postmenopausal women with ER+ve breast cancers (Goss *et al.* 2003, Coombes *et al.* 2004, Cuzick *et al.* 2010). It was therefore an apparently logical step to use aromatase inhibitors as adjuvant treatment for MBC.

In an analysis of 512 MBC cases derived from the SEER database, 124 (28%) received adjuvant endocrine therapy – tamoxifen alone (95), aromatase inhibitor alone (AI) (19), tamoxifen and AI (8) (Harlan *et al.* 2010).

Although cancer mortality was reduced in those receiving tamoxifen compared with no adjuvant therapy, there was no apparent benefit from adjuvant AIs. Investigation of 257 German MBC patients with ER+ve cancers revealed that 207 (81%) received tamoxifen and 50 (19%) were prescribed AIs (Eggemann *et al.* 2013). There had been 47 (18%) deaths in those given tamoxifen compared with 16 (32%) in the AI group after 42.2 months and following adjustment for age, tumour size, nodal status and tumour grade, the mortality among those given AIs was increased 1.5-fold.

The same group went on to retrospectively compare the outcomes of 316 FBC cases and 158 MBC cases treated with adjuvant tamoxifen, together with 60 FBC and 30 MBC cases given AIs (Eggemann *et al.* 2017). The 5-year OS rates of FBC and MBC patients were similar: 85.1% vs 89.2%. In contrast, FBC patients given AIs had significantly better survival compared with MBC given AIs, 85.0% vs 73.3% ($P=0.028$). The gender difference in efficacy of adjuvant AIs may relate to testicular oestrogen synthesis, which is unaffected by AIs (Doyen *et al.* 2010). Approximately 20% of male oestrogen originates from the testes. This means that if adjuvant AI is considered, this should be given in combination with a GnRH analogue to stop testicular stimulation by the hypothalamus. Unfortunately, this may lead to further and perhaps unacceptable side effects. Using neoadjuvant therapy means that, if ineffective, a switch of therapy can be instigated. If the neoadjuvant treatment works, the patient will be aware that the cancer is shrinking, which may serve as an encouragement to accept short-term side effects.

At present, the best available neoadjuvant endocrine treatment is tamoxifen, and there is a pressing need for multicentre international trials to determine the most appropriate duration of treatment and likelihood of allowing breast conserving surgery or enabling mastectomy in locally advanced MBC.

Conclusions

There are encouraging signs of international collaborations studying MBC so that there is an improvement in the understanding of the presentation and characterisation of the disease (Humphries *et al.* 2017, Vermeulen *et al.* 2017, Cardoso *et al.* 2018). It is also becoming clearer that obesity and the metabolic results thereof may play an important role in the development of MBC as result of decrease in androgens and increase in oestrogens. This forms a small part of the health problems arising from obesity but is yet another driver towards a healthier lifestyle.

MBC lags behind FBC in terms of public awareness and also rational treatment decisions. What is lacking is any evidence from RCTs conducted on MBC so that there is an overreliance on results from the multiple FBC trials, which may or may not be applicable to MBC. The hope for the future is collaboration with appropriately powered studies examining the neoadjuvant, adjuvant and palliative treatment for a rare but steadily increasing disease.

Declaration of interest

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