Conditions of the male breast: Gynaecomastia and male breast cancer (Review)

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Abstract. Breast disease most commonly affects females; however, a small percentage of men are also affected. Understandably given its low incidence, awareness of male breast disease is low, particularly among the general population. We searched the Medline database from 1950 onwards using the search terms male, breast, neoplasms and gynaecomastia, and reviewed the conditions associated with male breast disease, examining some of the risk factors and discussing how these conditions are diagnosed and treated, and finally putting forward some suggestions for their future management.

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1. Introduction

Breast disease most commonly affects females; however, a small percentage of men are also affected. Awareness of male breast disease, particularly among the general public, is low. Men do, however, possess a small amount of breast tissue, which makes them susceptible to breast disease, in particular male breast cancer (MBC) and the benign condition gynaecomastia (1,2). This review highlights some of the risk factors associated with the two conditions, and describes their diagnosis and treatment.

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2. Diagnosis and pathology

Male breast cancer. Breast cancer in men may be uncommon, but it does occur (3). Male breast cancer (MBC) is responsible for less than 1% of all breast cancers, though there is some variation in the literature as to the exact figure (3-5). This is in contrast to female breast cancer (FBC), which is the most common female cancer worldwide. According to figures from Cancer Research UK, approximately 300 men are diagnosed with MBC in the UK per year (6). This small number of cases has has made it impossible to set up randomised prospective international trials to determine the most effective way of managing MBC, and it is currently approached in the same way as FBC (7,8).

The incidence of MBC is rising, as reported in an age-corrected study conducted in the US, where increases of up to 26% were been noted between 1973 and 1998 (5). Unpublished data obtained from UK Cancer Registries suggest that the incidence in the UK is also increasing; this is reflected in figures obtained from Cancer Research UK (Fig. 1). There is, moreover, little evidence to suggest a positive change in the male mortality rate, while in females the mortality rate is decreasing. This may be due to the lack of a thorough understanding of MBC (9).

In the majority (75%) of cases, MBC patients present to their GP with a painless lump in the subareolar region of the breast, eccentric to the nipple (3,4,7,8). In some instances, patients may present with other symptoms, such as pain and nipple involvement. Pain is uncommon, occurring in only 5% of cases (1,4). Changes in the nipple can include nipple retraction, nipple discharge, and even ulceration (4). Although rare and occurring in only 1% of MBC cases, it is crucial to consider Paget's disease when relying on clinical features for diagnosis. Paget's disease is a type of breast cancer which originates in the ducts of the breast but spreads to the nipple, causing changes to the nipple skin. Its presentation is often similar to that of other skin conditions, such as eczema; reddening of the skin and itchiness is often observed, and bleeding and crusting is common (1,4).

The most frequently occurring type of MBC in terms of histology is invasive ductal carcinoma of no special type, which accounts for 90% of MBCs (4,10). Papillary carcinoma is the second most common type, with a 2-fold increased incidence in males compared to females (11). Most histopathological
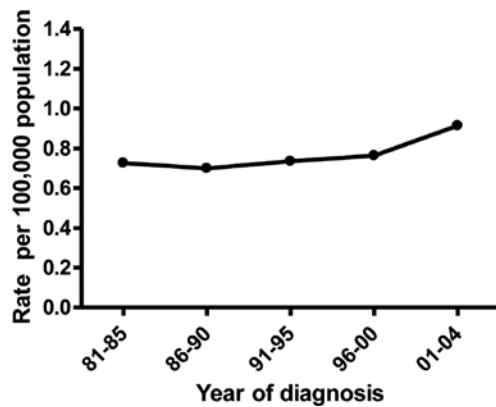
Figure 1. Age-standardised breast cancer incidence rates for the UK showing a gradual rise in incidence over the last ten years.

subtypes of breast cancer observed in females have also been reported in males; however, most men do not have well-developed lobules, making lobular carcinoma exceedingly rare (3,4,10). Ductal carcinoma *in situ*, often of a low grade, has been reported in 5-15% of cases (12). Hormone receptor expression is extremely common in MBC, with figures of up to 90% reported, compared to only 60-70% in FBC (3,13). Previous studies report that the rate of HER2 in MBC is similar to that found in FBC (14,15). However, due to the improved standardisation of HER2 testing, recent data indicate that HER2 amplification is infrequent in male breast tumours, accounting for only 5% of cases (16,17).

Gynaecomastia. Gynaecomastia is a condition involving benign proliferation of the glandular tissue in the male breast, resulting in non-cancerous breast enlargement (2,18). It is often associated with life stages characterised by significant hormonal imbalances, e.g., the neonatal period, puberty and old age (18). Neonates are at risk of gynaecomastia since they are exposed to high levels of estrogen from the mother's placenta. This type of gynaecomastia is known as transient, and is estimated to be present in 60-90% of neonates (18-20). Pubertal gynaecomastia affects 48-64% of boys. The cause is not fully understood, but is presumed to be due to an imbalance in estrogen and androgen. Gynaecomastia in late life is typically observed in men over 50 years of age. Traces of gynaecomastia reported in as many as 55% of autopsies suggest that it often goes undiagnosed (18-20).

The above-mentioned types of gynaecomastia associated with hormone imbalances are examples of true gynaecomastia. Another class of gynaecomastia is pseudo-gynaecomastia. Physical examination is required to differentiate between the two types (21). Pseudo-gynaecomastia is a condition where the male breast is enlarged due to the deposition of adipose tissue, and is often associated with obesity (2,21). In contrast, true gynaecomastia is an increase in the hyperplasia of the breast tissue. It often presents as a firm rubbery mass of tissue in the subareolar area. Although the mass is firm to the touch, it is usually not hard, and the lesion is commonly bilateral and symmetrical. However, in certain cases it can be unilateral and asymmetrical. As a similar presentation is commonly observed in MBC, in such cases further testing is required to rule out

cancer (2,8,18,20). Gynaecomastia is more common than breast cancer in the male population, with an estimated 40-65% of healthy males affected by the disease (18,20). Variations in numbers may be due to the interchangeable use of clinical and histological definitions, and due to controversy over what actually qualifies as clinical gynaecomastia. For example, Cakan and Kamat defined gynaecomastia as breast glandular tissue enlarged by ≥0.5 cm in diameter (19), while Daniels and Layer required patients to have breast tissue enlarged by ≥2 cm in diameter for a diagnosis of gynaecomastia to be made (22).

3. Risk factors

Male breast cancer. The rarity of MBC makes it difficult to determine the true causes of the disease; few studies have had a sufficiently large sample size to ensure significant findings (9). Fortunately, researchers can use information gathered from studies on FBC to design their studies and to determine whether the results are the same for MBC. There are many factors potentially linked to MBC (Table I), but these relationships need further investigation for significance to be determined.

A positive family history of breast cancer is found in approximately 20% of MBC patients, and increases the risk by as much as 3-fold (9,10,23). There are certain genetic mutations that show a clear association with MBC, and others that are in the early stages of investigation. Breast cancer in men is common in families that carry the *BRCA2* mutation. Most inherited MBCs are thought to be associated with a mutation in the *BRCA2* gene, which is reported to increase the risk of MBC by 80- to 100-fold compared with the general male population (24). This gene is located on chromosome 13q12-13 and is thought to be involved in DNA repair, as it is responsible for the regulation of the activity of the DNA repair gene *RAD51* (9,10,23,25). Despite this strong link, the percentage of individuals with a *BRCA2* mutation varies significantly among different populations. A study on Icelandic men found the *BRCA2* mutation in 40% of male cancer patients, whereas a study in California discovered the mutation in only 4% of patients. These figures could be influenced by small sample size, or could be indicative of genetic differences in individuals of different ethnic backgrounds (9,10,23).

Cowden syndrome is an autosomal dominant condition caused by a germline mutation in the *PTEN* gene that makes individuals susceptible to benign or malignant neoplasms. As *PTEN* is a tumour suppressor gene, any mutations of this gene prevent the suppression of tumours growing in the breast. It has been suggested that *PTEN* only plays a role in cancer in individuals affected by Cowden syndrome (2,23,25).

CHEK2 is another gene that is potentially associated with MBC. It is a cell-cycle checkpoint kinase and, like BRCA2, has a role in DNA repair. It has been proposed that CHEK2*1100delC, a variant identified by a CHEK2 Breast Cancer Consortium study, is responsible for up to 9% of MBCs and increases the risk of MBC by approximately 10-fold. However, other related studies that looked for the mutation globally in MBC have argued against this finding (5,9,23).

A study of germline mutations in the *androgen receptor* (*AR*) gene demonstrated a possible associated predisposition to MBC (26). Again, this finding is controversial; other studies claim that there is no significant evidence to support

Table I. Risk factors associated with male breast cancer (MBC).

Risk factor	Explanation
Age	Risk of MBC increases with age (5).
Ethnicity	Incidence of MBC seems to be higher in Ashkenazi Jews (1,4).
Genetics	Family history and *BRCA2* genetic mutations increase risk of MBC (23).
Childlessness	Having no children seems to increase the risk by 5-fold in comparison to men who have children, possibly related to infertility (hormonal) (8).
Environmental exposure	Some occupational hazards increase the risk of MBC (8).
Hormonal factors	Increased estrogen levels are related to MBC (23).

Table II. Summary of the main causes of gynaecomastia.

Cause	Explanation
Puberty	Transient hormone changes (56).
Hormonal imbalances	Hormone-based therapies, e.g. for the treatment of prostate cancer, have been associated withgynaecomastia (33).
Drugs (prescription and those of abuse)	No clear explanation in the absence of randomised trials (8,19,20,33).
Hepatic cirrhosis	Alcoholic cirrhosis (57).
Hypogonadism	Often secondary to Klinefelter's syndrome (58).
Testicular tumours	Tumours can elevate levels of estrogen and repress testosterone (59,60).
Hyperthyroidism	Estrogenic effects of active metabolites of dehydroepiandrosterone and its sulphate (61).
Chromosomal abnormalities	Klinefelter's syndrome is commonly associated with gynaecomastia (20).

This is a non-exhaustive list, and many of the conditions are inter-related

this link (9,23,27). Instead, it has been suggested that the *AR* gene contributes to MBC by affecting the ratio of estrogen and androgen (4,9,23).

CYP17 codes for cytochrome P450c17α, which is involved in estrogen and androgen biosynthesis. A polymorphism in this gene leads to an increase in steroid hormone production. As a result, it is believed to be a key gene in MBC. Further studies are needed using larger sample sizes to substantiate this association (4,9,23).

Evidence suggests that some occupational hazards increase the risk of employees developing breast cancer. Electromagnetic fields (EMFs) may affect workers by reducing the amount of melatonin produced by the pineal gland. Studies have found that melatonin may prevent the growth of breast cancer cells, and that reduced levels affect breast tumour development (23,28). Although these studies have shown an associated increase in risk, it is difficult to compare and relate the results, as measurements of the amount of exposure to EMFs were not noted (23). Additional occupational environmental factors linked to the increased risk of breast cancer have been proposed, but the exact mechanisms behind these links are unclear. These include high temperatures and environments characteristic of soap and perfume manufacturing (4,28).

Hormonal factors are arguably the main risk factor for MBC. Conditions such as liver cirrhosis and obesity can affect estrogen levels, and have therefore been considered as additional risk factors for MBC. Liver cirrhosis can result in the elevation of estrogen and the reduction of testosterone levels, which may predispose individuals to MBC. Studies by Sorensen *et al* showed a 4-fold increase in the risk of MBC in individuals with cirrhosis (29), although other researchers have suggested this increase is insignificant (30). However, this finding appears to be supported by a Swedish study, which found a difference in the incidence of MBC in alcoholics (31).

Obesity doubles the risk of MBC, as the condition results in increased estrogen production. There seems to be positive correlation between circulating estrogen and body weight (4,23). The increasing incidence of obesity is now a major problem in Western society, and the Department of Health in the UK estimates that by 2010 33% of men will be obese (32), with a possible concomitant rise in MBC (4,23).

Gynaecomastia. Gynaecomastia develops when there is an imbalance in estrogen and androgen levels; breast tissue growth is stimulated by estrogen, whereas androgens exert an inhibitory effect. There are a number of factors that can increase the risk of imbalance between these two hormones (20).

The main causes of gynaecomastia are presented in Table II. One of the most important factors associated with the condition is Kleinfelter's syndrome. Gynaecomastia is reported in approximately 80% of cases of Kleinfelter's syndrome (20). Some studies propose that the extra X chromosome in the XXY genotype is responsible for the increase in the risk of gynaecomastia and MBC (20). Various studies have found no significant evidence linking gynaecomastia and MBC (4,23). However, it is evident that Kleinfelter's syndrome does link the two conditions, as it is considered to cause both, and there is published data to suggest that individuals with Kleinfelter's have a 20- to 50-fold increased risk of MBC (4,20,21).

A number of drugs have been associated with the development of gynaecomastia, but the associated mechanisms are not fully understood. These drugs include illegal narcotics such as marijuana, heroin and amphetamines, but also many prescription drugs, such as peptic ulcer, cardiovascular and psychoactive drugs, and even antibiotics (8,19,20,33). More recently, it has been reported that HIV-positive patients tend to develop gynaecomastia as a result of HAART, an anti-HIV drug (34). These findings must be considered by health professionals when prescribing drugs to male patients for various medical conditions.

Familial gynaecomastia, a rarity with only a handful of cases reported worldwide (35-37), has been associated with functional abnormalities of the cytochrome p450 gene (*CYP19*). This gene encodes aromatase, one the key enzymes involved in estrogen biosynthesis.

4. Treatment

Male breast cancer
Treatment of localised disease. Treatment of MBC is usually very similar to that of FBC. Cancer in the early stages is usually treated with modified radical mastectomy and axillary node clearance. Recently, sentinel lymph node biopsy has been shown to be accurate and feasible in the treatment of clinically node-negative MBC (38). Several studies have also suggested that follow-up radiotherapy may be beneficial to men. A number of studies support this mode of treatment for preventing recurrence, but agree that it has no overall affect on survival (8,10).

Adjuvant hormonal therapy is an important factor in the treatment of MBC, since 90% of cases are hormone-receptor positive (4,5). Tamoxifen is the gold standard for early and advanced FBC (4,7,9), but its efficacy may be underestimated as most studies have been carried out for a maximum of 2 years, while in females tamoxifen has an optimum affect after 5 years of therapy (4). Tamoxifen is the first-line hormonal therapy for the treatment of hormone-positive primary male breast carcinoma. To date, there have been no randomised controlled trials investigating the MBC response rate to tamoxifen and any associated side effects. Previous reports suggest that tamoxifen treatment is safe and well tolerated by males. The agonistic effect of tamoxifen on the endometrium

is non-existent in men, and hot flushes, a common side effect in females, are less severe in male patients (5,39). However, its success does not mean that it is suitable in all cases, as tamoxifen leads to side effects in 62.5% of users (41). These side effects can range from mood changes and depression to more physical changes such as weight gain, hair loss and even impotence (4,8). A telephone survey showed that sexual dysfunction was the main cause of tamoxifen discontinuation in men (40). Newer aromatase inhibitors, which are proving superior to tamoxifen in a postmenopausal ERα⁺ setting in FBC (42-44), have yet to be fully investigated in MBC. However, there are encouraging early reports documenting the successful use of letrozole in the clinical setting in male subjects (45,46). These agents provide an additional treatment strategy for MBC. With respect to adjuvant chemotherapy, benefits have been reported in some MBC patients, but relatively few studies have been conducted to confirm these findings. Therefore, the risks need to be thoroughly assessed on a patient-specific basis (1,9).

Treatment of advanced disease. For decades, hormone treatment has been the main line therapy for advanced breast cancer in men. Ablative therapy (orchidectomy) and more recently hormone treatment have been applied with success in metastatic MBC; the latter is psychologically more acceptable to men, and is associated with lower morbidity (47,48). Tamoxifen remains the first-line treatment, but anastrazole and letrazole have produced some objective responses and are more likely to be widely used (45,49). Systemic chemotherapy is another option in the metastatic setting, but is usually a second- or third-line therapy since most tumours receive hormonal treatment. Chemotherapy is used in particular in patients with hormone-negative tumours. Response rates vary from 13% for single-agent fluouracil administration to as high as 67% for FAC combination therapy (48). No information exists regarding the use of trastuzumab in the adjuvant setting for advanced MBC, but in view of the remarkable benefits it has had in FBC the drug should also be used for the treatment of HER2-positive male breast tumours (4). As in FBC patients, sequential hormone and chemotherapy treatment is preferred to concurrent administration (4).

Gynaecomastia
Treatment. The treatment of gynaecomastia depends on the cause. When it results from a primary condition, it needs to be addressed and treated. In about 25% of cases, there is no underlying cause, so treatment is necessary only in the event of patient distress such as embarrassment or pain (19,20). Two selective estrogen receptor modulators (SERMS) have been evaluated for the treatment of gynaecomastia. Of these, tamoxifen has shown high efficacy, leading to the complete regression of gynaecomastia in approximately 70% of cases (20,21). Raloxifene was effective in reducing the size of pubertal gynaecomastia; however, this finding was demonstrated in an uncontrolled study involving 10 cases (50). A randomised, double blind, placebo-controlled trial found the effects of the aromatase inhibitor anastrozole ineffective in reducing pubertal gynaecomastia (51). Despite encouraging results with SERMS, surgery is still the preferred mode of treatment for gynaecomastia. Recently, less invasive surgical techniques have been introduced, including mammotome

excision of gynaecomastia under ultrasound guidance (52). However, surgical intervention is not recommended for pubertal gynaecomastia until puberty is complete, as hormonal imbalances can cause recurrence, and as 80% of cases spontaneously resolve within 2 years (18,19).

5. Conclusions

Gynaecomastia is a relatively common benign enlargement of the male breast. The relationship between gynaecomastia and MBC has been investigated, but to date there is no convincing evidence that gynaecomastia is associated with a higher risk of MBC development. The incidence of MBC is increasing, and further research is required to fully understand its cause and subsequent treatment. Considering that the incidence of obesity is also increasing significantly and doubles the risk of MBC, research on obesity and obesity prevention programmes may be interlinked with MBC (23,32). MBC also has a strong genetic link, in particular with *BRCA2*. Other as yet unidentified genes may also be linked to MBC. These may include FGFR2, TNRC9, MAP3K1 and LSP1, which were identified by SNP analysis as susceptibility genes in FBC (53). Large multicentre collaborative studies are required to extrapolate these findings to MBC and to confirm any significant relationships.

It is crucial to foster an awareness of MBC, not only to enable early diagnosis, but also to avoid the stigmatisation and to reduce the psychological burden experienced by many MBC patients (1,54,55).

Acknowledgements

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