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CLINICAL REVIEW

Gynaecomastia and breast cancer in men

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Sources and selection criteria

We searched Medline for English language papers with the key words "gynaecomastia", "gynecomastia", and "male breast cancer"; the Cochrane database for clinical trials; our personal archives of references; and websites with those terms. We also referred to our institutional experience with gynaecomastia and male breast cancer.

Breast disorders in males can be distressing for both patients and examining doctors. Patients often feel embarrassed and anxious. Although cancers are diagnosed in only about 1% of cases of male breast enlargement, practitioners may feel uncertain about how to differentiate gynaecomastia (benign breast enlargement) from malignancy and how to manage these disorders. This review covers the causes, evaluation, and treatment of gynaecomastia and of breast cancer in males.

What is gynaecomastia?

Gynaecomastia is the benign enlargement of male breast tissue (>2 cm palpable, firm, subareolar gland and ductal tissue) resulting from a relative decrease in androgen effect or increase in oestrogen effect. Breast enlargement due to adipose tissue is called pseudogynaecomastia.

How do hormones affect the breast?

Male breast tissue contains receptors for androgen, oestrogen, and progesterone. Oestrogen stimulates duct development and progesterone stimulates alveolar development in the presence of the permissive anterior pituitary hormones luteinising hormone, follicle stimulating hormone, and growth hormone. Androgens antagonise the effects of oestrogen. A high prolactin level does not stimulate breast tissue growth but alters the production of luteinising hormone by suppressing production of gonadotrophin hormone releasing hormone.

What are the hormone sources in men?

Testicular Leydig cells produce 95% of testosterone. The adrenal cortex produces the rest. About 50% of circulating testosterone is bound to sex hormone binding globulin. Much of the remainder is weakly bound to albumin. Only the free hormone is active. Oestrogen is less bound to sex hormone binding globulin than testosterone, so increases in sex hormone binding globulin reduce the ratio of active testosterone to oestrogen.

Testosterone can be converted to another potent androgen, dihydrotestosterone, by the enzyme 5 α reductase in peripheral tissues. Testosterone also can be converted to oestradiol by the enzyme aromatase, found especially in adipose tissue. The weak adrenal androgen androstenedione can be converted by aromatase to oestrone, a weak oestrogen. Oestradiol and oestrone can be interconverted in peripheral tissues (see fig 1 on bmj.com).

When is gynaecomastia physiological?

Overall, 65-90% of neonates have breast tissue, which results from the transfer of maternal and placental oestrogen and progesterone and persists up to several months.

By age 14 up to 60% of boys have gynaecomastia. This usually resolves within one or two years (table 1). At puberty, surges of luteinising hormone and follicle stimulating hormone in conjunction with growth hormone and insulin-like growth factor-1 stimulate testosterone production in Leydig cells. Oestrogen concentrations increase threefold, peaking earlier than testosterone concentrations that eventually increase up to 30-fold. Whether gynaecomastia results from the relative delay in full testosterone production, a temporary increase in aromatase activity, varying sensitivity to oestrogen, or all of these is uncertain.

Gynaecomastia increases with age as free testosterone levels decline and obesity becomes more common (table 1).[1] In an unselected group of men admitted to hospital, the prevalence and diameter of breast enlargement was highly correlated with increasing body mass index.[2] Autopsy studies have found gynaecomastia in 40-55% of unselected cases.[3]

What disorders or drugs enlarge the breast?

Non-physiological gynaecomastia develops with disorders or drugs associated with low testosterone levels, high testosterone conversion to oestrogen, high oestrogen levels, and high sex hormone binding globulin levels resulting in low free testosterone (see boxes).

Drugs, creams, cosmetics, and lotions

Body builders who use high doses of androgen frequently develop significant gynaecomastia, often with breast tenderness, because of androgen conversion to oestrogen.[4] At the opposite end of the spectrum, men

Tips for non-specialists

Breast tissue is a common finding in males and is almost always benign in newborns, at puberty, and in otherwise healthy older men, especially if they are obese

If the physical examination is suspicious for cancer (see table 3), then refer for biopsy

prescribed combined gonadotrophin releasing hormone agonist-androgen receptor antagonist therapy or androgen receptor antagonist monotherapy for prostate cancer develop gynaecomastia 10-20% and 50-60% of the time, respectively.[5] Gynaecomastia is much less common in men taking 5 α reductase inhibitors for benign prostatic hypertrophy (0.3-1.1%).

Patients treated with highly active antiretroviral therapy for HIV report gynaecomastia, but the prevalence and mechanisms are uncertain.[6] Pseudogynaecomastia can occur in patients with HIV associated lipodystrophy. HIV does not increase the risk for breast cancer, but HIV associated lymphoma can present as a lymphomatous breast mass.

Cosmetics, creams, and lotions may contain oestrogens or compounds with oestrogen effects. Children are particularly vulnerable to these sources. Three healthy prepubertal boys developed gynaecomastia, which was traced to repeated application of a "healing balm" containing lavender oil (*Lavandula augustifolia*), lavender scented soap and skin lotions, and shampoo and styling gel containing lavender and tea tree oil (*Melaleuca alternifolia*), respectively. Antiandrogenic effects of lavender and tea tree oil were confirmed using human breast cancer cell lines.[7] Gynaecomastia resolved within a few months of stopping these applications.

Starvation and refeeding

Children and adults refed after starvation or given growth hormone can develop transient gynaecomastia. The mechanisms are thought to be similar to those governing gynaecomastia during puberty.

Illness

Multiple mechanisms may operate in systemic diseases. Thyrotoxicosis increases production of androstenedione, oestrogen production in peripheral tissue, and sex hormone binding globulin levels. Androgen catabolism is reduced in liver disease, making more available for conversion to oestrogen in peripheral tissue. Renal failure has many effects on hormone and drug metabolism.

Diseases associated with gynaecomastia

Low androgen levels

Hypogonadotrophic hypogonadism (Kallmann's syndrome); high prolactin states; pituitary disease; primary hypogonadism—infection (viral orchitis), trauma, infiltration (haemachromatosis), chemotherapy, neurological disease (spinal cord injury, myotonic dystrophy); Klinefelter's syndrome; true hermaphrodism; congenital defects in testosterone synthesis

High androgen and high oestrogen levels

Testicular feminisation, Leydig cell tumour, human chorionic gonadotrophin producing tumour, congenital adrenal hyperplasia

High oestrogen levels

Abnormal aromatase (activating mutation), tumour aromatase, feminising adrenal carcinoma, Sertoli cell tumour, starvation and refeeding

High sex hormone binding globulin levels leading to low free testosterone levels

High oestrogen states, genetic high sex hormone binding globulin level, hyperthyroidism

Other or multifactorial

Cirrhosis, renal failure, idiopathic

Table 1 | Prevalence of gynaecomastia

Age group	Percentage with gynaecomastia
Neonates	65-90
Puberty (age 14)	60
16-20 years	19
25-45 years	33-41
>50 years	55-60

Tumours

All types of testicular tumours have increased aromatase activity.[8] Leydig and Sertoli cell tumours produce androgen and oestrogen. Germ cell tumours produce intratesticular human chorionic gonadotrophin, which can cause dysfunction of Leydig cells and reduced testosterone production. Lung and hepatic tumours can produce enough systemic human chorionic gonadotrophin to increase Leydig cell testosterone secretion, which is readily converted to oestrogen through increased aromatase activity. Gynaecomastia may follow cancer treatment if chemotherapy or radiation damages Leydig cells.

Genetic causes

Several families (fathers and sons) have been described with oestrogen excess due to mutations activating the aromatase gene.[9] They developed prepubertal gynaecomastia and accelerated prepubertal growth.

Who is at higher risk for breast cancer?

Table 2 lists the conditions associated with breast cancer in males.

Male breast cancer represents about 1% of all cases of breast cancer, but in sub-Saharan Africa 7-14% of breast cancer cases occur in men. Population based US tumour registries show that rates are highest in African-American men, intermediate in non-Hispanic Caucasian men and Asian-Pacific Islanders, and lowest in Hispanic men.[10] Male breast cancer can occur at any age but mean age is 65 years.

The risk of gynaecomastia and breast cancer coexists in high oestrogen states. Men with Klinefelter's syndrome have a 58-fold higher risk than normal males for breast cancer, with an absolute risk that approaches 3%.[11] Breast cancer has been reported in male to female transsexuals who were castrated and given high dose oestrogen. In one nested case-control study of 41 Swedish men who developed breast cancer after treatment for prostate cancer, the risk was higher in men treated with oestrogen than in other survivors.[12]

A family history of breast cancer increases the risk of breast cancer in males. In some families this is linked to the breast cancer risk gene BRCA2. Ashkenazi Jews have a higher prevalence of BRCA1 and BRCA2 and an increased risk of male breast cancer than the general population.[13] Male carriers of BRCA2 have a

Drugs associated with gynaecomastia

Low androgen levels: inhibition of testosterone synthesis

Ketoconazole; metronidazole; gonadotrophin releasing hormone agonists (chronic) and antagonists; spironolactone; chemotherapy (cytotoxic drugs)

Low androgen levels: inhibition of testosterone action

Androgen receptor blockers—bicalutamide, flutamide, nilutamide, spironolactone, eplerinone, cyproterone; 5 α reductase inhibitors—finasteride, dutasteride; H_2 blockers and proton pump inhibitors—cimetidine, ranitidine, proton pump inhibitors; marijuana

High androgen levels resulting in high oestrogen levels

Androgen administration—excessive testosterone replacement, anabolic steroids, androgen containing contraceptives; human chorionic gonadotrophin

High oestrogen levels or oestrogen action

Oestrogen administration; occupational exposure to oestrogen; oestrogen containing creams or cosmetics; isoflavones; phytoestrogens—cosmetics, soy products, beer, tea tree oil, lavender oil; oestrogen action—diethylstilbesterol, clomiphene, phenytoin, digitalis

Other or multifactorial

Angiotensin converting enzyme inhibitors, alcohol, amiloride, amiodarone, amphetamines, calcium channel blockers, ciclosporin, diazepam, growth hormone, highly active antiretroviral therapy, heroin, methyldopa, isoniazid, reserpine, risperidone, theophylline, tricyclic antidepressants (increase prolactin levels)

cumulative risk for breast cancer of 7% by age 80. The excess risk in male carriers of BRCA1 is much less.

Exposure to ionising radiation may also increase the risk of breast cancer. The incidence of breast cancer is higher in male survivors of cancer who have received therapeutic chest irradiation, particularly at a young age. The rate of breast cancer in Japanese men exposed to nuclear fallout was threefold greater than in non-exposed men.[14]

How should male breast tissue be evaluated?

Table 3 lists differences in the presentation of gynaecomastia and malignancy. If breast tissue enlargement is unilateral, a diagnosis other than gynaecomastia must be considered. In the absence of exogenous androgen or other drugs, rapid development of breast enlargement outside puberty suggests a tumour producing luteinising hormone or human chorionic gonadotrophin. Almost no lobular tissue exists in normal adult male breast tissue. Gynaecomastia is characterised by proliferation of ductules and loose connective tissue. Increasing glandular tissue in adult men increases the concern for malignancy.

Other important physical findings include adiposity, signs of hyperthyroidism, liver disease, hypogonadism (gynoid body habitus, decreased body hair, small testes consistent with Klinefelter's syndrome), excessive musculature indicating exogenous androgen administration, or a testicular mass.

Initial laboratory evaluation

If the cause of breast enlargement is not obvious, laboratory evaluation is needed (fig 2). Such evaluation is unnecessary for boys at puberty, for typical asymptomatic senile changes, for enlargement consisting mostly of adipose tissue, for men taking drugs known to cause gynaecomastia, or for physical findings strongly suggesting breast cancer.

Imaging

Imaging is not necessary if cancer is not suspected. Ultrasonography and mammography can, however, differentiate adipose tissue from gynaecomastia and can be useful if surgical intervention is planned. Mammography is about 90% sensitive and 90% specific for malignant compared with benign masses in men.[15] Invasive cancers are solid on ultrasonography. A complex cystic mass also is suspicious.

Biopsy

Biopsy is the only way to make a definitive diagnosis. Patients with a hard, irregular or asymmetrical mass, nipple discharge (bloody or non-bloody), axillary adenopathy, or a mass fixed to skin or the chest wall must have a biopsy (table 3). Core biopsy is recommended over fine needle or excisional biopsy. Most primary breast carcinomas in men are ductal, either invasive or non-invasive (ductal carcinoma in situ).[16] Papillary histology is more common and lobular histology is rare in men (see fig 3 on bmj.com). Ninety per cent of breast cancers in men have oestrogen and progesterone receptors.

Metastatic and non-malignant breast masses

Rare causes of male breast masses include metastatic carcinoma from lung, prostate, and liver; haematological malignancies, including lymphoma, Hodgkin's disease, and plasmacytoma; and benign conditions, including myofibroblastoma, papillary hyperplasia, lupus mastitis, haemangioma, hamartoma, and granulomatous mastitis.

When and how should gynaecomastia be treated?

Physiological gynaecomastia requires no treatment unless accompanied by pain or significant embarrassment. Withdrawing an offending drug or treating an underlying disorder may be sufficient, especially if gynaecomastia is relatively recent.

Testosterone replacement for hypogonadal men can be beneficial, but longstanding fibrotic gynaecomastia is unlikely to respond. One small study showed more

Table 2 | Risk factors for male breast cancer

Category	High risk established	High risk suggested
Oestrogen excess	Klinefelter's syndrome, exogenous oestrogen	Cirrhosis
Androgen deficiency	Cryptorchidism, orchitis, orchiectomy	
Ethnic and familial	Family with history of breast cancer; sub-Saharan African	Ashkenazi Jew
Specific genes	BRCA2, BRCA1	Androgen receptor mutation, CHEK2* mutation, CYP17† mutation, PTEN‡ mutation
Exposures	Radiation	Electromagnetic fields, occupational, polycyclic aromatic hydrocarbons

*Cell cycle checkpoint kinase regulating responses to DNA damage.
†Cytochrome P450c17a gene coding enzyme involved in oestrogen and androgen synthesis.
‡Tumour suppressor gene associated with Cowden syndrome, an autosomal dominant susceptibility to multiple hamartomas.

Table 3 | Physical examination in male breast enlargement

Gynaecomastia	Malignancy
Bilateral (usually) or unilateral	Unilateral (usually) or bilateral
Painless or painful (occasionally)	Painless or painful (uncommon)
Central (subareolar)	Central (70-90%) or eccentric*
Smooth	Irregular*
Firm	Rubbery or hard*
Mobile	Fixed†
Normal nipple	Nipple deformity (17-30%) or discharge (<10%)*
Normal skin	Thickened, red, or ulcerated skin*
Normal axilla	Axillary adenopathy†

*Mandates surgical evaluation.
†May be associated with locally advanced malignancy.

stable testosterone levels and more resolution of gynaecomastia with transdermal testosterone than with biweekly intramuscular testosterone injections that resulted in high initial testosterone levels with potential to cause high oestrogen levels.[17] Danazol, a weak androgen, is less effective.

Anti-oestrogen treatment with tamoxifen 10-20 mg/day significantly reduced pain and breast volume in 40-80% of boys with persistent pubertal gynaecomastia[18] and men with prostate cancer treated with an androgen receptor blocker (bicalutamide).[19] Trials of raloxifene and clomiphene are too small or results too mixed to be conclusive. The aromatase inhibitor anastrazole was no better than placebo for reducing breast volume during puberty[20] and was less effective than tamoxifen in men treated with bicalutamide.[19]

Local irradiation (10-12 Gy) prevented gynaecomastia in men with prostate cancer treated with bicalutamide,[20] but tamoxifen achieved significantly better results.[21]

Surgical treatment

Men with findings suspicious for malignancy or gynaecomastia causing persistent pain or embarrassment should be referred to a surgeon. Goals of surgery include removing abnormal breast tissue, restoring the normal male breast contour, and reducing pain.

Liposuction is effective if breast enlargement is mostly caused by adipose tissue and the overlying skin is fairly taut. Subcutaneous mastectomy is required for removal of glandular tissue and redundant skin (visible inframammary skinfolds) and pain relief. Complications include haematoma, seroma, infection, sensory changes, pain, breast asymmetry, skin redundancy, and scarring.[22,23] The most common complication is a poor cosmetic outcome. Final results of surgery may not be apparent for a year.

How is male breast cancer treated?

No prospective studies have been done of male breast cancer. Management is extrapolated from female breast cancer and from case series in single institutions.

Questions for future research

What is the best treatment for painful gynaecomastia?

Should breast cancer in men be treated differently from that in women?

Which hormone therapy is most appropriate for male breast cancer in the adjuvant setting?

What is the role for immunotherapy or anti-angiogenesis therapy in men with aggressive or refractory breast cancer?

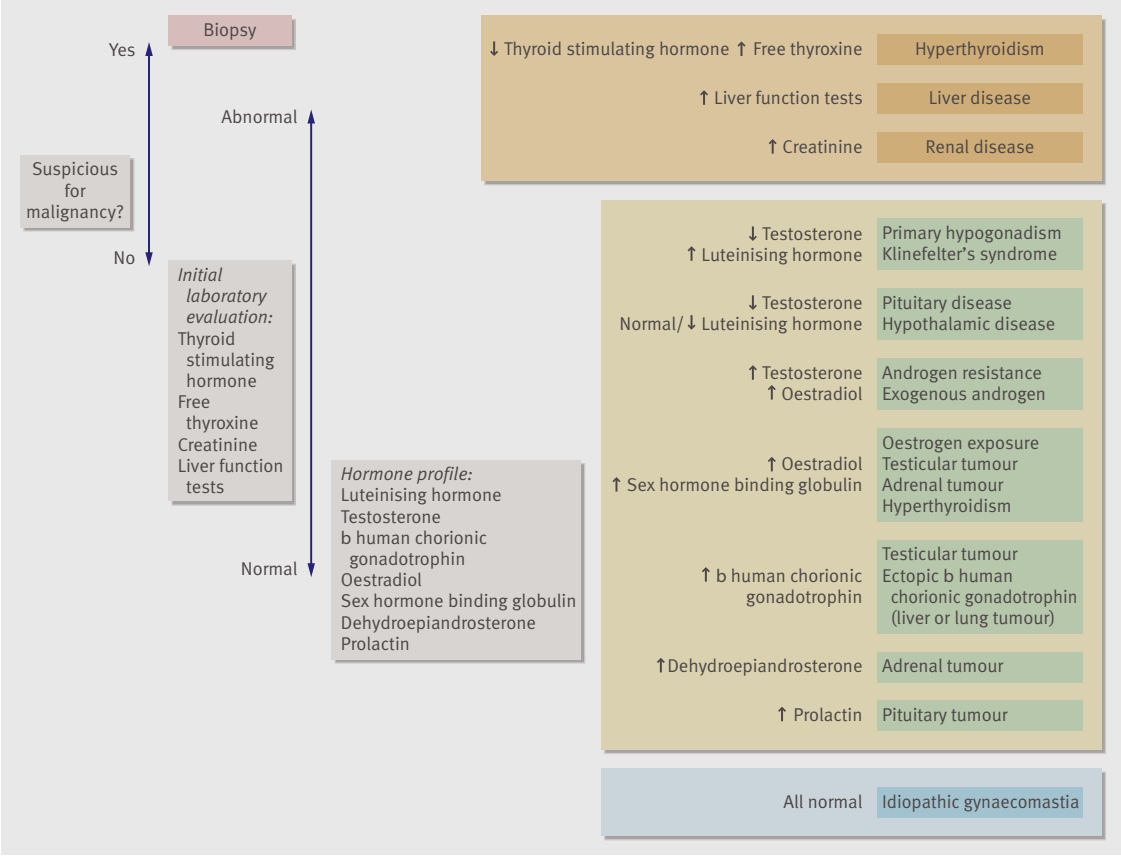

Fig 2 | Evaluation of non-physiological breast enlargement in men when cause is not obvious

Patient vignette

A 33 year old man mentioned fatigue; headaches; painful, enlarged breasts; and impotence. He had been a heavy user of androgen containing substances for muscle enhancement until three months previously. Examination revealed moderate obesity; normal visual fields; 7 cm tender, firm palpable subareolar breast tissue on the left and 4 cm non-tender tissue on the right; and soft 5 ml testes bilaterally. Levels of follicle stimulating hormone, luteinising hormone, and testosterone were low. His prolactin level was mildly elevated. Magnetic resonance imaging showed a 5 mm pituitary mass. Levels of thyroid stimulating hormone, free thyroxine, morning cortisol, and adrenocorticotrophic hormone were normal.
A mammogram showed noticeably increased glandular tissue, especially on the left.

Gynaecomastia was thought primarily to be due to conversion of previous high dose androgen to oestrogen in adipose tissue. Suppression of the hypothalamic-pituitary-gonadal axis can persist for months to years after prolonged exposure to exogenous androgen. Prolactin induced suppression of the gonadotrophin releasing hormone pulse generator may have contributed. The patient was given a dopamine agonist (cabergoline) to suppress prolactin. Levels of follicle stimulating hormone, luteinising hormone, and testosterone remained low. Transdermal testosterone caused skin irritation. Biweekly intramuscular testosterone reduced fatigue, but the high peak testosterone levels increased oestrogen levels, which, in turn, increased prolactin levels. He developed more gynaecomastia (to 6 cm) and pain in his right breast. He refused tamoxifen. He has been referred to a surgeon because of ongoing breast pain.

Local surgical management is modified radical mastectomy (simple mastectomy plus axillary dissection or sentinel node biopsy), with postoperative radiation for bulky tumour, involved or close margins, clinically positive nodes, or inflammatory carcinoma.

Men usually are offered adjuvant hormone therapy with tamoxifen 20 mg/day for five years, as several retrospective studies have shown improved survival.[24] If the tumour has adverse features, adjuvant systemic therapy (chemotherapy or HER2 antibody trastuzumab, or both) should be offered. Experience of using adjuvant aromatase inhibitors in men is limited. The management of metastatic and recurrent disease is similar to that in women.

Men are less likely to be diagnosed as having breast cancer at an early stage, but diagnosis at the preinvasive (in situ) stage has increased since the 1980s.[18]

When men and women are matched for tumour stage and histology, no sex difference is found in tumour specific survival. Overall survival is shorter in men, possibly because they tend to be older and have more comorbid conditions.

SUMMARY POINTS

Most breast enlargement in males is due to the benign enlargement of breast tissue (gynaecomastia)

Physiological gynaecomastia occurs in neonates, at puberty, and with obesity and ageing

Gynaecomastia is due to an increased oestrogen to testosterone ratio; possible causes are many

Treatments for painful or embarrassing gynaecomastia include an anti-oestrogen, such as tamoxifen, or surgery (liposuction or mammoplasty)

One per cent of breast cancers occur in men, with higher rates in men with a family history of breast cancer or previous chest radiation

Irregular, eccentric, hard or fixed breast tissue, ulceration, nipple abnormalities, or associated adenopathy suggest breast cancer

Men typically have more advanced breast cancer at diagnosis than women; management is similar

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