BCUK Briefing | Breast Cancer in Men

SUMMARY

Breast cancer in men is much rarer than in women, mainly because men have less breast tissue and lower lifetime oestrogen exposure. Most UK patients are diagnosed between the ages of 60-70. Around 10% carry a mutated BRCA2 gene and ~7% have Kleinfelter's syndrome. Exposure to elevated oestrogen is a key risk factor, and may be a result of genetics, illness or lifestyle factors. Obesity and physical inactivity are important risk factors. Heavy drinking, radiation, exposure to occupational carcinogens and endocrine disrupting chemicals may also increase risk. Most cases are invasive ductal carcinoma and oestrogen receptor positive. Treatment generally involves surgery with or without drug and/or radiation therapy.

Introduction

Breast cancer in men accounts for less than 1% of all cancer cases diagnosed in men worldwide, including the UK. It is an understudied disease – most of our understanding comes from the study of breast cancer in women. The sexes share many similarities, but there are also notable differences; most of which are not translated into clinical practice. Recent years have seen a rise in targeted research of breast cancer in men with new evidence deepening our understanding. This brief summarises the major characteristics of breast cancer in men, including incidence, risk factors and treatment. For brevity we refer to breast cancer in men by the acronym MBC (Male Breast Cancer).

How common is breast cancer in men?

Breast cancer is about 100 times less common in men than in women (1). In 2019, 25,143 men were diagnosed with breast cancer worldwide, and there were 12,099 deaths from the disease(2). According to the latest statistics from 2016-18, 375 men in the UK were diagnosed with the disease, and 32 with ductal carcinoma in-situ, a non-invasive cancer that remains in the breast ducts. Eighty-four men died because of their breast cancer, 49% of whom were over 75 years old (3).

The age standardised incidence rate for MBC in the UK is 1.3 cases per 100,000 men (4). Rates are similar in most developed countries, and generally higher than in those that are less developed (where rates of breast cancer in women are also lower; 5, 6). By comparison, breast cancer is the most common female cancer in most countries around the world, including the UK, where the age standardised incidence rate is 169 cases per 100,000 women (7). Since the mid-1990s, incidence rates of MBC in the UK have remained stable for most age groups, except for the age group of 65-69. Over a 23-year period, the incidence rate in this group has risen by 38% from an age-standardised rate of 2.4 per 100,000 men in 1993-1995 to 3.6 per 100,000 men in 2016-2018 (8). This has been reflected in a recent Scottish study over a 25-year period (1992 to 2017) showing the rising incidence of breast cancer with age, peaking in men aged 65-70 and 75-79 years (9).

Racial patterns of breast cancer are also dissimilar between the sexes. Recent data from the US shows that the age-standardised incidence rate of breast cancer in non-Hispanic black men is up to 2.6 times higher compared to non-Hispanic white men, depending on the subtype. For oestrogen receptor positive / HER2 negative breast cancer, incidence in black men is 1.4 times that of white men. In contrast, incidence of the same type of breast cancer in black women is 0.79 times that of white women (10).

What are the most common symptoms of breast cancer in men?

Breast cancer develops in the small amount of breast tissue men have behind their nipples. The most common symptom is a hard, painless, rubbery, and immobile lump in one breast, growing around or under the nipple. A cancerous lump will also usually feel uneven rather than smooth. Other symptoms may include an inverted nipple, nipple discharge, pain, sores, and/or enlarged lymph nodes under the arm (11, 12).

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Why don't more men get breast cancer?

Men are far less likely to get breast cancer than women due to their lack of breast tissue, and much lower levels of oestrogen in their blood (known as circulating oestrogen), compared to pre-menopausal women (13). This is mainly because oestrogen encourages a high rate of cell division which increases the risk of mutations, including those that lead to breast cancer. Elevated lifetime exposure to oestrogen is a well-established breast cancer risk factor (14).

Does the type of breast cancer and age of onset differ between the sexes?

Like most cancers, the greatest risk factor for MBC is age; most UK patients are diagnosed between the ages of 60-70. Data from the US suggest that on average, this is 5-10 years later than age at diagnosis in women (15). At the time of diagnosis, men tend to have more advanced features e.g. larger tumour size, lymph node involvement and or regional or distant metastasis (17). Late diagnosis is partly attributable to lack of awareness and screening programs, but also indicates gender-specific differences (16).

Over 90% of breast cancers in men are Invasive breast cancer of "no special type", or"invasive ductal carcinoma", where cancer cells have grown through the lining of the ducts into surrounding breast tissue. In women around 70% are this type (18). Ductal carcinoma in-situ, an early form of breast cancer which remains localised to the ducts, occurs in < 10% of cases. Papillary carcinomas are the second most common histological type of invasive breast cancer in men, while lobular and metaplastic carcinomas are extremely rare (19, 20).

Around 91-95% of breast cancers in men are oestrogen receptor positive (21). In women this number is around 75% (22, 23). Breast cancers in men are also typically progesterone receptor positive, HER2 (human epidermal growth factor 2) receptor negative, and responsive to endocrine therapy. Triple negative breast cancer in men is extremely rare (24).

Are risk factors for breast cancer the same for both sexes?

Several risk factors for breast cancer in women are associated with reproduction and will not apply to men. Others associated with age, genetics, hormones and the environment are shared, but there is some variation. Sometimes men can develop glandular breast tissue similar to that found in women, due to underlying conditions such as Klinefelter's syndrome, abnormal blood hormone levels or use of certain medications, which may put them at a higher risk (25).

Gynaecomastia is a common abnormality of the male breast, with 57% of men over 44 years of age having visible excess breast tissue. True gynaecomastia is a benign growth of the ducts and stromal tissue of the breast. Pseudo gynaecomastia is a proliferation of fatty tissue in overweight/obese men. Both are often accompanied by pain, while cancerous breast tumours in men are often painless (26). There is no strong evidence of gynaecomastia increasing risk of MBC (27).

Hormones

Oestrogen has a major role in the development of MBC, through binding and activating the oestrogen receptor protein (28). Breast cancers in both sexes also typically express receptors for androgens (e.g. testosterone). Androgens are hormones that influence reproductive activity and growth in both sexes, but primarily in men. In oestrogen receptor positive breast cancer in both sexes, androgen receptors are almost always expressed (29-31). The ratio of circulating levels of oestrogen and androgen is crucial in healthy functioning of breast tissue. Disruption to this balance can be a consequence of several conditions such as liver damage, Klinefelter's syndrome and testicular dysfunction, all of which may lead to MBC (32).

Liver damage (or cirrhosis) causes increased conversion of the androgen, androstenedione, to oestrone, oestradiol and testosterone. Subsequently,

testosterone is converted back to androstenedione and oestrone, causing abnormally low plasma levels of testosterone and elevated androstenedione and oestradiol, almost to the same levels as in females. This imbalance may initiate MBC (33).

Klinefelter's syndrome is a chromosomal disorder where men inherit an extra X chromosome, in addition to the normal XY chromosomes. It affects around 1 in 660 newborn boys (34). Those with this syndrome are at 20-50-fold increased breast cancer risk, accounting for up to 7% of all breast cancers in men. They have elevated plasma levels of oestradiol, luteinizing hormone, and follicle-stimulating hormone, with very low levels of testosterone. This hormonal imbalance is thought to lead to a proliferation of ductal breast cells leading to carcinogenesis (35, 36). The median age of diagnosis of breast cancer in men with Klinefelter's syndrome is the same as for other men, suggesting the condition does not accelerate the progression of breast cancer (37). The breast cancer mortality rate of these individuals is similar to that of women (38-40).

Other conditions specific to men that result in lower levels of circulating androgens and elevated breast cancer risk include: testicular inflammation (known as orchitis); surgical removal of testes; undescended testes (known as cryptorchidism), inflammation of the epididymis (known as epididymitis) and testicular damage due to occupational exposure (e.g. working with hot furnaces) (41-43).

A prior history of orchitis or epididymitis has been proven to elevate breast cancer risk in a 2010 US Veterans study (44). Studies suggest that men with cryptorchidism or orchitis and who have never fathered children also carry a higher risk of developing breast cancer (45). It has been suggested that men suffering from these conditions may benefit from testosterone replacement therapy to counter the risk of breast cancer (46).

Exogenous hormones, especially used in gender reassignment, have also been implicated as a significant risk factor. Trans women (assigned male at birth with female gender identity) have a 46-fold increased risk of breast cancer compared to cisgender men (assigned male at birth with male gender identify) (47).

Genetics

Genetics plays a significant role in breast cancer risk in both sexes, but differences exist here too. There can be several genetic factors predisposing men to developing breast cancer, which primarily include germline mutations in the BRCA2 gene. Family history is also important; around 15-20% of men who develop breast cancer have first degree relative(s) (parents, siblings, and children) with the disease (48, 49).

Germline mutations: At least 10% of breast cancer cases in men are associated with inheriting a single mutated (also known as high penetrance) breast cancer susceptibility gene such as BRCA2, responsible for around 10% of all MBC, and BRCA1, responsible for 1-2% of MBC (50, 51). In comparison, around 7-10% of breast cancers in women are associated with inheriting a single mutated high penetrance gene (52. 53) with mutated BRCA genes responsible for around 4-6% of female breast cancers (1.5-3.7% for BRCA1 and 2.5-3.5% for BRCA2).

Men who carry mutations in BRCA2 (a gene involved in repair of DNA damage) have up to 10% (1 in 10) lifetime risk of developing breast cancer (54, 55). By contrast, the average man has a lifetime risk of approximately 0.1% (1 in 1000) (56, 57). In addition, BRCA2 associated breast cancer in men is more likely to be of higher stage and grade, as well as being more prone to lymph nodal metastasis and hormone receptor positivity (58). In contrast, germline mutations in BRCA1 are less common and a weaker risk factor for MBC (59).

Patients with prostate cancer also have a greater chance of developing breast cancer; this may be because prostate cancer belongs to a group of cancers including breast, ovarian and pancreatic,

that are linked by heritable BRCA2 mutations (60). BRCA1 and BRCA2 carriers were found to be at an elevated risk of developing both breast (especially oestrogen receptor positive) and prostate cancer in the largest case-control study done to date on men carrying these mutations (61). Similarly, men with a family history of these cancers may be at an increased risk.

Germline mutations in several other genes are recognised as risk factors for MBC (62). Approximately 2-5% of breast cancer patients referred for genetic testing have mutations in genes classified as "moderate penetrance" genes, meaning they confer a moderate risk of breast cancer which can be modified, to some extent, by environmental factors or clinical treatment (63). The most significant example of such a gene in breast cancer in men is PALB2, which interacts closely with BRCA1 and BRCA2. (64). Men with PALB2 germline mutations have a 0.9% (1 in 111) risk of developing breast cancer in their lifetime (65). Other notable examples of moderate penetrance genes that affect MBC include CHEK2, ATM, PIK3CA, RAD51C, and RAD51D (66-68).

Lifestyle factors

Smoking: Even though cigarette smoking is a known risk factors for many cancers, and a likely risk factor for breast cancer in women (69), there is very little evidence to suggest a similar role in MBC. In an analysis from the Male Breast Cancer Pooling Project, which included 1483 patients, tobacco exposure was not found to be associated with breast cancer risk (70). However, a more recent study did find that smoking significantly reduces overall survival in men with breast cancer, with smokers approximately 3 times more likely to succumb to the disease earlier than non-smokers (71). Some evidence suggests passive smoking may increase MBC risk (72).

Alcohol Consumption: There is little evidence to suggest that low-moderate alcohol consumption increases breast cancer risk in men. The Male Breast Cancer Pooling Project study that investigated this found no association between increased risk of MBC and average alcohol consumption under 60 gm/day. However, an association was observed between high alcohol consumption of >60 gm/day (~ ¾ bottle of wine/day) and an increased risk of MBC (73, 74).

Obesity and Physical Activity: Obesity is linked to increased risk of MBC. Results from the Male Breast Cancer Pooling Project found risk was increased by around 30%: similar to that seen for women (75). Obesity in men leads to a doubling of oestrogen production compared to men with an average BMI (body mass index). Reduced testosterone levels and increased oestradiol in the blood plasma have also been observed in men with BMIs >35. Both these factors contribute to the genesis of breast cancer in men with high BMIs (76, 77). In addition, a considerable shift to a sedentary lifestyle as well as rising obesity levels since the late 1990s is a contributing factor to increased incidence of MBC (78), with the numbers of men receiving a breast cancer diagnosis apparently paralleling rising levels of obesity (79). The Nordic Occupational Cancer Study found increased physical workload to have a 20-25% protective effect against breast cancer in men, with the effect being stronger with increased physical activity (80). Data from the Canadian Occupational Disease Surveillance System have found similar effects, with increased incidence of breast cancer in men with sedentary occupations such as administrative roles (81).

Occupational and Environmental Exposures

Radiation exposure is a known risk factor for many cancers, including breast cancer. Repeated or lengthy exposure to diagnostic radiographs or radiation therapy increases the risk of MBC (82). A study examining male incidence and mortality of breast cancer in atomic bomb survivors found a much higher radiation-associated relative risk of breast cancer in men than in women (83).

There is evidence that MBC is associated with exposure to environmental pollutants, including

carcinogens and endocrine disrupting chemicals (EDCs). This is especially true for oestrogen mimicking chemicals (84), which induce similar actions to those of oestrogen and have been linked to increased breast cancer risk and other health problems including prostate cancer. For further details please see our EDCs and breast cancer.

Certain occupations may also carry a higher risk of breast cancer. For example, motor vehicle mechanics have a higher breast cancer incidence. This may be associated with occupational exposures to petrol and petroleum solvents, established carcinogens such as polyaromatic hydrocarbons, and known EDCs such as alkylphenols (85, 86). Men who work in high temperature environments such as blast furnaces and steel works also have an elevated risk of breast cancer (87, 88). The reason for this is most likely temperature affecting testicular function, thus affecting oestrogen levels.

A 1991 study also found an elevated risk of breast cancer in men who were continually exposed to electromagnetic fields for over 30 years, and risk was increased 3-6-fold in electric power workers, electricians, and telephone linemen (89). Later meta-analyses have confirmed that exposure to electromagnetic fields increases the risk of MBC (90, 91). Grundy et al. have also shown that men with occupational exposure to magnetic fields are at a higher risk of breast cancer than men with only background exposure (92). In comparison, most studies find women are not at increased risk from electromagnetic field exposure (93).

One study examining occupational exposures in those employed in the 1960s and 1970s found that men who worked in factories that manufactured perfumes and soaps were more than seven times more likely to develop breast cancer than the male population at large (94). The authors suggest that this may be a result of exposure to oestrogen mimicking chemicals, commonly used in these products. The same study found men involved in the print and newspaper industry had elevated breast cancer rates. At the time, newspapers were not produced digitally; the increased risk may have been a consequence of exposure to EDCs in ink.

Long-term consumption of contaminated drinking water by men living at a marine corps base in North Carolina was shown to result in higher incidence of breast cancer (95). Contaminants included the volatile organic compound 1,2, dichloroethylene, tetrachloroethylene, an EDC (96) and suspected carcinogen (97), and vinyl chloride, a known carcinogen (98). A recent Scandinavian study has also found constant occupational exposure to trichloroethylene for more than six months doubles the risk of breast cancer in men (99).

How is breast cancer in men treated?

To date, no breast cancer clinical trials have been done that target men specifically, although men are now starting to be included alongside women in some trials. Consequently, treatment is largely based on population-based data or extrapolation from treatment recommendations for women, with minor variations (100). Generally treating breast cancer involves surgery with or without drug and/or radiation therapy. The extent of disease is a key factor in deciding the best treatment – if cancer has spread beyond the breast, drug therapies are usually recommended (101).

In early stage localised breast cancer, the standard surgical procedure offered to men is modified radical mastectomy which involves removal of the affected breast tissue and nipple. This is usually accompanied by removal of glands under the nearby armpit and or muscle underneath the breast, called axillary lymphadenectomy. Although unusual, breast conserving surgery with lumpectomy and adjuvant radiotherapy may also be offered. Outcomes with both these treatment approaches are comparable to those of women (102, 103). Recent data on breast conservation surgery in men suggests that it may be a safer alternative to modified radical mastectomy (104).

Radiation therapy post-mastectomy in men remains a debated topic due to the dearth of clinical trial evidence (105). However, retrospective studies have shown improved survival and decreased local recurrence in men who underwent radiation therapy both post-mastectomy and breast conserving surgery, especially in node-positive disease (106, 107). If there is local recurrence post-surgery, radiotherapy and systemic anti-cancer therapy may be considered after excision of the recurrent tumour

Adjuvant therapy (therapy given in addition to primary surgery with curative intent) is offered as endocrine therapy, chemotherapy, and human epidermal growth factor receptor 2 (HER2)-directed therapy, depending on the type of breast cancer (109). Endocrine therapy is usually recommended as 91-95% of MBC are oestrogen receptor positive, and the oestrogen receptor blocking drug, tamoxifen, also used to treat women, is commonly used (110). Most patients will undergo at least 5 years of adjuvant endocrine therapy to reduce this risk of disease recurrence (111).

Chemotherapy may be offered if the disease is higher grade or stage and if it is oestrogen receptor negative and/or HER2 receptor positive. The standard chemotherapy regimens used to manage metastatic breast cancer in men are CMF (cyclophosphamide and methotrexate and fluorouracil), CAF (cyclophosphamide and doxorubicin and fluorouracil) and more recently AC/AC-T (doxorubicin and cyclophosphamide with or without a taxane), as per those used with curative intent for breast cancer in women (112).

Chemotherapy may also be used to help relieve symptoms and improve prognosis in incurable disease (113, 114) and a retrospective study from 2015 has also reported significant anti-tumour activity on administration of anthracycline (115). Recent data indicates that men with hormone positive breast cancer with distant metastasis who have received surgery, radiation therapy, and drug therapy (i.e. chemotherapy, Anti-HER2 therapy, hormone therapy, as appropriate), have a significant survival advantage over men who received only drug therapy, especially in men with HER2 positive breast cancer (116), which has a worse prognosis in terms of survival compared to men with HER negative disease (117).

There are ongoing research efforts into the potential clinical benefit of therapies targeting a protein family called poly-ADP-ribose-polymerase (PARP) involved in DNA damage repair pathways. Administration of the PARP inhibitor Olaparib has shown promising results in BRCA-mutated prostate cancer (118) and there are good data for its benefit in patients with germline BRCA mutation associated breast cancers both in the adjuvant (119) and metastastic settings (120). Although not yet approved for clinical use, modulation of androgen receptor (AR) activity is also an area of intensive research as a promising therapeutic target for MBC (121, 122).

Conclusion

It is difficult to estimate the number of cases of breast cancer in men that might be prevented. As for breast cancer in women, obesity is a modifiable risk factor, which could be avoided with diet and exercise. Heavy alcohol consumption may increase risk: reducing consumption will also help prevent weight gain. Physical activity is especially important, as it has been shown to be protective against breast cancer in men. Occupational exposures to known carcinogens and endocrine disrupting chemicals and prolonged electromagnetic field exposures are also thought to be risk factors. A healthy lifestyle and strong health and safety measures in certain workplace settings may reduce the risk of MBC.

In the UK, breast cancer in men has increased by around 20% over the past 50 years (123). It is estimated that men have a 1 in 870 lifetime chance of getting breast cancer (124). Although this figure is much lower than the corresponding figure for women, who have a 1 in 7 chance over their lifetime, breast cancer in men should be more recognised and every effort made to reduce its incidence.

Glossary

- **AC/AC-T: Chemotherapy regimen** – doxorubicin plus cyclophosphamide with/without a taxane
- **Androgen receptor positive**: breast cancer cells that have androgen receptors
- **Androgen receptor**: protein that binds androgen
- **Androgen**: sex hormone associated with male sexual and reproductive function, and the development of masculine traits; also present in women
- **Aromatase inhibitors**: Class of drugs that inhibit the enzyme aromatase
- **ATM**: Ataxia-telangiectasia mutated. Helps cell growth control and DNA damage repair.
- **BRCA1** and **BRCA2:** breast cancer susceptibility genes; a BRCA1 or BRCA2 mutation affects ability to repair DNA; increases breast cancer risk
- **CAF**: Chemotherapy regimen – cyclophosphamide plus doxorubicin and fluorouracil
- **Carcinogen**: substance or agent that can cause cancer
- **Carcinoma in situ**: non-invasive tumour that has not spread
- **CHEK2**: Checkpoint kinase 2. Prevents cells from growing and dividing too quickly.
- **Chemotherapy:** the treatment of disease by the use of chemical substances, especially the treatment of cancer by cytotoxic and other drugs
- **CMF: Chemotherapy regimen** – cyclophosphamide plus methotrexate and fluorouracil
- **Endocrine disrupting chemical** (EDC): any chemical that can interfere with hormone functions in humans and/or animals and have adverse effects
- **Endocrine (hormone) therapy:** slows or stops the growth of hormone-sensitive tumours by blocking the body's ability to produce hormones or by interfering with effects of hormones on breast cancer cells.
- **HER2 positive**: breast cancer cells that have HER2
- **HER2**: Human epidermal growth factor receptor 2 (type of receptor binding human epidermal growth factor)
- **Klinefelter's syndrome**: rare genetic condition; males have an extra X chromosome (XXY); affects sexual development
- **Lymph node**: rounded mass of tissue containing immune cells; lymph passes through, is filtered and cleaned
- **Malignant**: tumour that has become invasive and spread to other sites in the body
- **Metaplastic carcinoma**: cancer that begins in cells that have changed into another cell type
- **Metastasis**: The spread of cancer cells from the place where they first formed to another part of the body.
- **Mutation**: change in hereditary material (DNA) in a cell
- **Oestrogen mimicking chemical**: a type of EDC, often a synthetic compound, that imitates natural oestrogen and triggers the same biological actions
- **Oestrogen receptor positive**: breast cancer cells that have oestrogen receptors and grow in response to oestrogen
- **Oestrogen receptor**: protein that binds oestrogen; binding triggers pathways that lead to increased cell multiplication
- **Oestrogen**: principal female sex hormone associated with breast development and reproduction; also present in men
- **PALB2**: Partner and localizer of the BRCA2. Works with the BRCA2 protein in DNA damage repair.
- **PARP inhibitors**: Class of drugs blocking the action of PARP proteins (e.g., Olaparib)
- **PARP**: Protein family called poly-ADP-ribose-polymerase. Involved in DNA damage repair pathways.
- **PIK3CA**: Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Alpha. Influences basic cellular functions like cell death, growth, and proliferation.
- **RAD51C and RAD51D**: RAD51 homolog C and D. Involved in DNA damage repair pathways.
- **Tamoxifen**: drug used to treat oestrogen receptor positive breast cancer
- **Tumour**: a mass of cells formed by uncontrolled cell division

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About Breast Cancer UK

Who are we?

Breast Cancer UK aims to prevent breast cancer through scientific research, collaboration, education and policy change. We educate and raise awareness of the risk factors for breast cancer and provide practical information to help people reduce these risks. We campaign to ensure government policies support the prevention of breast cancer. And we fund scientific research that helps to better understand what risk factors contribute to breast cancer, and how to address them

For further information on breast cancer risk factors please visit our website www.breastcanceruk.org.uk
To view this information in a more accessible format or to provide feedback, please contact us.

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