



Male breast cancer is not congruent with the female disease

Male breast cancer is almost always oestrogen receptor positive, and is traditionally treated in line with guidelines for treating hormone-sensitive breast cancers in postmenopausal women. **Ian Fentiman** questions the rationale for this approach, pointing to key biological differences between male and female breast cancers.

This is an abridged version of Ian Fentiman (2016) Male breast cancer is not congruent with the female disease. Crit Rev Oncol Hematol 101:119–124, doi: <http://dx.doi.org/10.1016/j.critrevonc.2016.02.017>. It was edited by Sophie Fessl and is published with permission © Elsevier



Only one percent of all breast cancer cases in the western world occur in men. With such a limited number of patients, no randomised trials for male breast cancer (MBC) are carried out, and treatment standards for men have been extrapolated from trials for female breast cancer (FBC). When looking closer at the data available, it becomes clear that aspects of MBC do not fit the model that men have endocrine-sensitive tumours that behave like tumours in postmenopausal women. Differences between breast cancer in men and women are seen in their epi-

demiological risk factors, molecular profiles and response to systemic therapy.

Risk factors

Endocrine risk factors

The Male Breast Cancer Pooling Project pooled risk factor data from 2,400 men with breast cancer from 21 studies, and identified obesity and gynaecomastia as risk factors (*JNCI* 2014, 106:djt465). The strongest predictor of MBC risk was found to be recent BMI.

MBC is almost always oestrogen

receptor positive (ER+). In a report pooling data from 1,483 patients, tumours were ER+ in 92% of patients, but HER2+ in only 5% (*Cancer Res* 2015, 75 (9):S6-05-S6-05). The frequency of FBC that are ER+ varies with menopausal status, but the proportion typically lies between 64% and 79% (*JCO* 1984, 2:1102–9). Around 10% of FBC are HER2+ (*PNAS* 2003, 100:8418–23).

Conflicting results have been reported for intratumoural aromatase; while a study of four MBC tumours found that MBC contained aromatase more

Take home messages from the author

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“For years, it has been argued that male breast cancer (MBC) is equivalent to female breast cancer (FBC). But the picture is much more complex. Importantly, tumour type differs between men and women. In more than 90% of MBC patients the tumour is oestrogen receptor positive (ER+). In FBC, 60–70% of tumours are ER+. The molecular profile also differs: 43% of FBC tumours are of the luminal A type, 20% luminal B, 10% HER2+ and 36% basal. The picture is completely different with MBC: 80–90% of tumours are luminal A, around 20% luminal B, and both HER2+ and basal types occur very rarely. This has implications for the treatments we should be using.

Clinical implications

Because MBC is rare, no randomised trials are carried out. Treatment recommendations are based on trials of FBC. But while aromatase inhibitors (AIs) are better for treating postmenopausal women than tamoxifen, analyses of male patients shows that men do not fare equally well when given AIs. If AIs are given to treat MBC, oestrogen production must also be blocked centrally with a GnRH analogue.

Further challenges

Collaboration is key to building our understanding of MBC. We need to work together to achieve structured treatment and carry out randomised trials to know how best to treat it.”

frequently than FBC (*Horm Cancer* 2013, 4:1–11), a report of 45 cases found only a third of MBC tumours expressing intratumoural aromatase, compared with 62% of FBC tumours (*Breast Cancer Res Treat* 2007, 105:169–175; *ibid* 1998, 49:S93–S99).

Genetics

Several genes associated with a high lifetime risk of breast cancer in women have been identified. One of these, *BRCA2*, confers a significant risk in men, equating to a 7% cumulative risk of breast cancer by the age of 80 (*Am J Hum Genet* 2001, 68: 410–419). *BRCA2* mutations are much more common than *BRCA1* mutations in MBC. Compared with FBC, a larger proportion of MBC are *BRCA2* tumours (10% of MBC cases), and a smaller proportion (1%) are *BRCA1* tumours (*Breast Cancer Res*

Treat 2012, 134:411–8).

Genome-wide association studies have identified single nucleotide polymorphisms (SNPs) that influence FBC risk. Of the 12 SNPs most strongly associated with FBC, five were also strongly associated with MBC (*PLoS Genet* 2011, 9:e1002290). Two of these – rs13387042 (2q35) and rs3803882 (*TOX3*) – were even more strongly associated with MBC than with FBC.

Epigenetics

MicroRNAs are short, 21–25 nucleotide long, molecules which do not encode proteins. They bind to complementary sequences in messenger RNA and control gene expression. A comparison of miRNA expression between 23 cases of MBC and 10 of FBC showed that miRNA expression signatures differ between male and female breast cancer.

MBC is characterised largely by under-expressed miRNAs (*Breast Cancer Res* 2009, 11:R58).

Molecular profile of MBC

Prognosis is significantly worse for MBC than FBC, largely due to tumour size and lymph node status (*Mod Pathol* 2002, 15:853–61). Molecular profiling shows that fewer than 1,000 genes are differentially expressed between MBC and FBC. Major processes, including energy metabolism, regulation of translation, matrix remodelling and immune recruitment are modulated differently. The androgen receptor plays a major role in MBC, while the progesterone receptor and HER2 are less important (*Breast Cancer Res Treat* 2011, 127:601–10).

The most common phenotype of MBC is luminal A, estimated to occur in 75–98% of MBC patients. This is followed by luminal B, with a frequency of 0–20%. Basal phenotype is rare, occurring in between 0% and 2% of patients, while no HER2+ tumours were found (*Breast Cancer Res* 2009, 11:R28; *Breast Cancer Res Treat* 2012, 133:949–958; *Mod Pathol* 2012, 25:398–404; *Acta Oncol* 2013, 52:102–109). An analysis of molecular subtypes of FBC in three studies shows that, in female patients, 43% of cancers are of the type luminal A, 20% luminal B, 10% HER2+ and 36% basal (*PNAS* 2003, 100:8418–23). Molecular profiles indicate that FBC and MBC are very different diseases.

Cell cycle proteins

Alterations in the expression of cell cycle proteins appear to play an important role in the development of MBC.

The kinase inhibitor proteins (KIPs) p27Kip1 and p21Waf1 negatively regulate progression of the cell cycle. Immunostaining of tumours shows that they are differently expressed in MBC and FBC (*Ann Oncol* 2002, 13:895–902).

p21Waf1 and p27Kip1 are expressed in 70% and 96% of MBC patients, respectively, while they are expressed in only 29% and 39% of FBC patients.

Chemotherapy

A comparison of US Veterans Administration data on 612 MBC patients and 2,413 FBC patients showed that patients with MBC received less chemotherapy. Median overall survival for patients with MBC was 7 years, compared with 9.8 years for patients with FBC (*Cancer* 2007, 109:1471–7).

A retrospective cohort study of 135 men treated between 1944 and 2001 showed a non-significant reduction in mortality in men with node-positive disease who were treated with adjuvant chemotherapy, mostly anthracycline-based. Survival was significantly improved in patients given adjuvant

hormonal therapy (*Cancer* 2005, 104:2359–64).

Endocrine therapy

Endocrine therapy is used as adjuvant, neoadjuvant and preventive treatment in FBC. Tamoxifen is used in the treatment of women before menopause. In women after menopause, aromatase inhibitors are given as adjuvant or neoadjuvant (*Cancer* 2007, 109:1471–7).

Because of the success of tamoxifen as a treatment for early FBC, tamoxifen was also used as an adjuvant in MBC. One study of 39 men with node-positive MBC given adjuvant tamoxifen showed that five-year survival was 61%, compared with 44% in historical controls (*Br J Cancer* 1992, 65:252–4). However, a study from Sloan-Kettering Memorial Hospital showed that tamoxifen use leads to side effects in two thirds of

MBC patients (*Cancer* 1994, 74:74–7). About one in four patients drop out (*ibid*; *Ann Oncol* 2011, 23:1471–4; *Curr Oncol* 2010, 17:17–21).

Aromatase inhibitors (AIs) are also used to treat MBC patients, especially with advanced or metastatic disease. In women, AIs are better than tamoxifen in terms of disease free survival and overall survival. However, evidence increasingly shows that AIs are less effective in male patients. While a study of 23 MBC patients who received AIs reported a partial response in 26% of patients and disease stabilisation in 57% (*Br J Cancer* 2013, 108:2259–63), a comparison of registry data in Germany of 257 MBC patients reported that the mortality rate was 1.5-fold higher among patients treated with an AI than among those treated with tamoxifen (*Breast Cancer Res Treat* 2013, 137:465–70).

To Smile



"It's got to come out, of course, but that doesn't address the deeper problem."