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GENETICRISKFACTORSBIOLOGYPSYCHOSOCIALASPECTSANDCOMPARISONBETWEENMALEBREASTCANCERANDFEMALEBREASTCANCER

Strictly as per the compliance and regulations of:

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Conclusion: Increased input is needed for informative and psychological support for MBC patients. Public education should be oriented. Toward men at higher risk to reduce symptom duration before diagnosis.

I. Introduction

Male breast cancer is a relatively rare disease, which accounts for less than 1% of all instances of cancer in men and about 1% of all breast cancer cases (1- 7). It accounts for less than 0.2% of all cancer related deaths among men (8- 11). Because of the rarity of the disease, most information about male breast cancer has been obtained from small, mono-centric, retrospective studies or through extrapolation from randomized prospective studies or from clinical experience of breast cancer in women (12). But this enormous volume of data on female breast cancer may not be completely relevant to men, particularly with regard to differences concerning the hormonal environment for men and women, and also in terms of gender differences that may affect the cancer patient's condition, medical and/or psychosocial side effects from treatments, and survival priorities.

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II. Method

This study is a systematic review of the literature. The literature review was conducted in order to describe the current state of knowledge and to compile the scientific literature within the field of breast cancer in men. The study processes the scientific papers in a systematic manner, which consisted of both empirical studies of quantitative and qualitative design, and theoretical or meta-analytic and overview studies. All of them had a clear link to breast cancer in men. The search for scientific literature was conducted in the PubMed database by searching for the key words "male breast cancer" and some articles were also selected from bibliographies from other publications.

Articles that were included in this study meet these criteria

- Articles in English language published between 1990-01-01 and 2013-09-30.
- Articles were about primary breast cancer in men.
- Articles touched heredity and genetic aspects, clinical features, clinical histopathology, diagnosis and diagnostic methods (mammography, ultrasound, fine needle aspiration biopsy / core needle biopsy and sentinel lymph node biopsy), treatment (surgery, radiotherapy, hormone therapy and chemotherapy), prognosis (prognostic factors and survival), and psychosocial aspects.
- Articles made a clear comparison of breast cancer in men and breast cancer in women

Articles were excluded if one or more of the following criteria were matched

- Articles that were case studies or studies with less than 10 patients (with the exception of case studies of unknown / rare genetic factors to MBC or articles with qualitative approach and in-depth interviews).
- Articles that affected other aspects of MBC disease including local epidemiological aspects and demographic patterns, studies of environmental risk factors or the effects of various drugs and medications or relationship between MBC and races, research into the mechanisms of MBC

tumors in cell level and in molecular subgroups or if a special or rare MBC tumor, etc.

– Articles that were studies of a certain group of people e.g. breast cancer in transsexual men or in HIV-infected men.
– Articles that were about MBC metastasis.
– Of the total of 812 articles, 187 were included in this review study that deals with genetic aspect, histopathology, and psychosocial aspects of MBC and also comparison between MBC and FBC.

III. Results and Discussion

a) Heritability and genetic aspects

The interaction between genetic and environmental factors generally, is probably of major importance for the occurrence of MBC (13). Most known risk factors related to genetic predisposition include positive family history, BRCA gene mutations and Klinefelter's syndrome (14).

Several studies indicate that a family history of breast cancer is associated with greater risk of MBC (15 -22). Approximately 15% to 20% of male patients with breast cancer have a positive family history (12-13). Quite a large percentage of MBC patients have a history of breast cancer in first-degree relatives (13, 19, 20, 23-27). A positive family history of either male or female breast cancer among first-degree relatives leads to 2-3 times higher risk of the emergence of MBC (9, 21, 23, 25, 28). This risk increases with increasing numbers of affected first-degree relatives and the early onset of breast cancer in the affected relatives (28). There is a strong correlation between heritable mutations in BRCA and the risk of MBC, but BRCA2 mutations are far more frequent than BRCA1 mutations in MBC cases (13, 27-32). BRCA2 mutations in MBC patients have been assessed in several studies and in various countries (13, 26-27, 33-47) and the results vary between 3% and 40% (Figure 1). These studies suggest that the frequency of BRCA2 mutations may reflect the possible genetic differences between different populations but caution should be exercised in interpreting these estimates, because of the small sample populations in the studies (9) or possible selection bias (18). The estimated lifetime risk of breast cancer among male BRCA2 mutation carriers is 5-10%, compared with a 0.1% risk of MBC in the general male population, i.e. 50-100 times higher (48). Moreover, the cumulative risk of MBC in BRCA2 mutation carriers is always higher than in non-carriers, and in all age-groups, but it is highest among those in their thirties (1,500 times higher) and in their forties (630 times higher) and lowest for those in their eighties (69 times higher) (28, 29). A recent multi-centric study from Italy by Ottini et al. (2012) (30) has shown that BRCA2 is correlated with aggressive tumour behaviour and with higher tumour grade.

Klinefelter's syndrome is also strongly associated with breast cancer in men (9, 33). The syndrome is characterized by a rare chromosomal abnormality, 47 XXY, with breast growth, small testes, infertility and increased excretion of follicle-stimulating hormone (FSH) (33), which occurs in less than one man per thousand (9) .The mean age of breast cancer patients with Klinefelter's syndrome is 58, which is slightly lower than the average age for other male breast cancer patients (9, 33, 50). Up to 7% of men with breast cancer may have Klinefelter's syndrome (33, 51-53). Compared with the frequency of the disease in the general population, breast cancer can be at least 20 times more common in these men (3, 9, 54). Other less known genetic mutations that have been reported in men with breast cancer include Reifenstein syndrome or androgen receptor (AR) mutations (55), CYP17 polymorphism (56), Li-Fraumeni syndrome or p53 or CHEK2 mutation (57 -59), Cowden syndrome or PTEN mutation (60) and Lynch syndrome or HNPCC (61), but the correlation between these mutations and increased risk of MBC has not yet been adequately researched (32, 62).

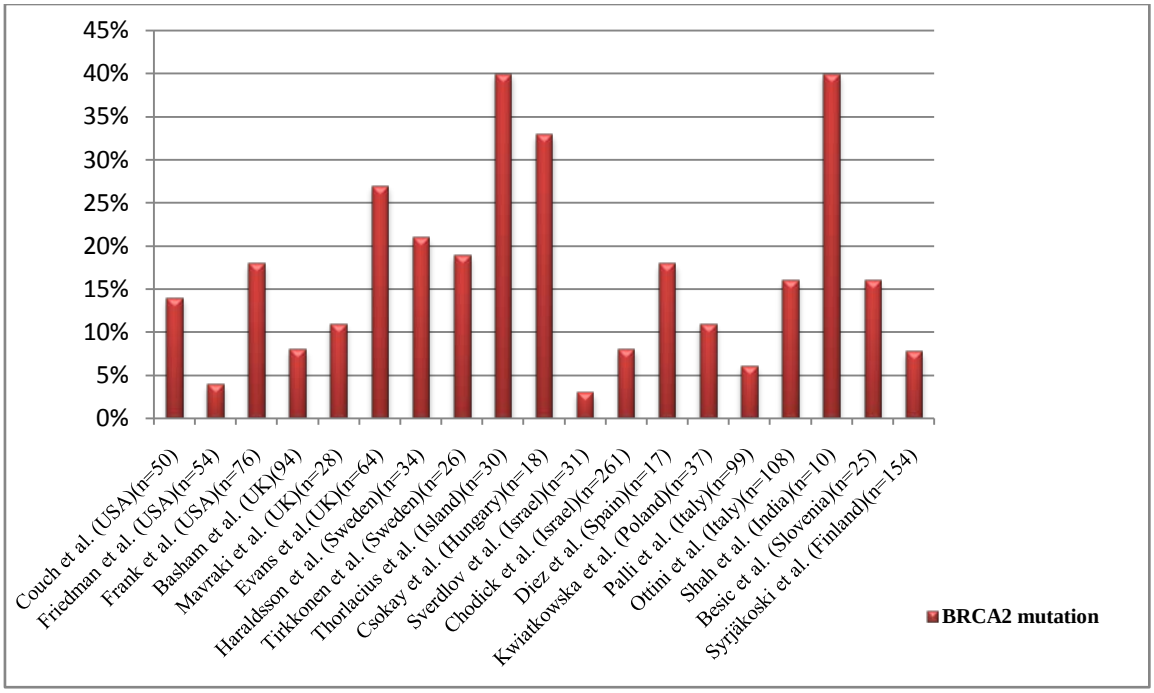

Figure 1 : BRCA2 mutations (%) in MBC patients in different studies and in different countries, with the number of participants in the studies

b) Histopathology

Almost all histopathological types of breast cancer have been identified in men (32, 63). The most common type is invasive ductal carcinoma, which is at least 80% in several studies (10, 14, 63-71) and ductal carcinoma in-situ (DCIS) is far less common, less than 10% (1, 63, 69, 72-74). A study by Lanitis et al. (2008) (75) showed that in-situ cancer in men is not as rare as reported in earlier studies, which indicates earlier detection of breast cancer in men (72). Rare tumour types include invasive papillary and medullary lesions (3) and Paget's disease (3, 62) and lobular breast tumours (3, 69, 76-78). Male breast tumours are usually sensitive to the hormones oestrogen and progesterone (10, 76, 79, 80, 81-87), which has been reported at between 55-92% for oestrogen and 39-89% for progestrogen for MBC cases in large, retrospective series (63, 69, 88-89) (Figure 2). Lymph node involvement in the armpit is very frequent, from 41% to 57% in large retrospective series (10, 90- 96) and 11-20% of male breast tumours grade I, 55-61% grade II and 22-33% grade III have been reported in large retrospective series (95-94, 81) Generally, 5-15% of MBC patients have metastases at diagnosis (6, 64, 76, 81, 97-98) but the numbers are higher in African and Asian series, i.e. up to 30% (71, 99-101). Details of the growth factor HER2 from various studies are highly variable and up to 56% of male breast tumours display an over-expression of HER2 (12, 43, , 57, 102-107).

c) Psycho-social aspects

The general perception of breast cancer as a female disease causes surprise in many men when they are diagnosed with breast cancer (77). France et al. (2000) (108) described in their study that men with breast cancer have been shocked to get a breast cancer diagnosis. These patients have not been aware that men can also be affected by such a disease, which is associated with femininity and they have found it difficult to understand that the disease can develop in a male body. Patients have also had difficulty revealing their breast cancer diagnosis to those around them. Iredale et al. (2005) (109) have described in their study that men with breast cancer are afraid of others' reactions, which reduce or question their masculinity. These patients were also uncertain about discussing this sensitive topic with those around them (109). However, when these patients try to talk about it with their friends and colleagues, the reaction becomes distrust and often a subject for fun in a lamentable way (77).

A sense of frustration also occurs due to a lack of relevant information about breast cancer in men (108-113). Men with breast cancer are more vulnerable in social contacts in comparison with female breast cancer patients (114), which leads to high levels of disease-specific stress (111). The cancer impact and cancer-related stress are worse in young MBC patients compared to those who are older (111, 115). Concerns about masculinity, fear of stigma and experience of isolation are associated with the general lack of knowledge and information about the disease (111). Different experiences of breast cancer care have also been reported by men and women in a study by Sime (2012) (116).

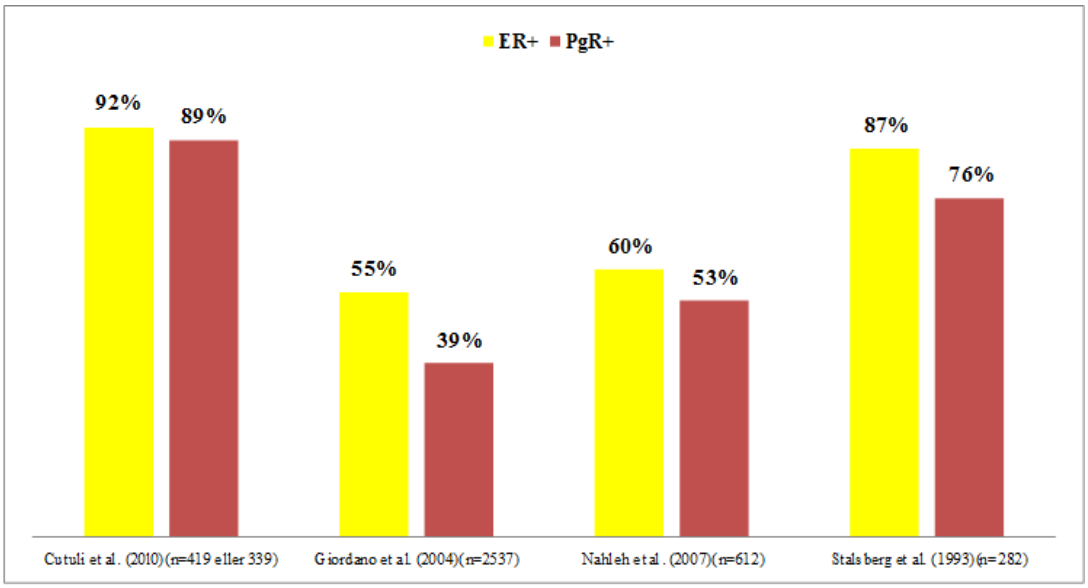

Figure 2 : Positive oestrogen/progesterone receptor (ER+ and PgR+) (%) in male breast tumours in some large retrospective series

d) Comparison between MBC and FBC

MBC and FBC differ mostly with regard to incidence figures, age at diagnosis, frequency of histological tumour types and frequency of expression of hormone receptors (5). The incidence of male breast cancer varies. Some studies report an increase in MBC in a few countries (4, 69, 77, 117-119). However, the incidence of female breast cancer (FBC) has been found to be increasing in most countries (50,102, 120) The incidence of breast cancer in men has been stable in Europe for several decades (121) and a new international population-based study by Miao et al. (2011) (120) also shows that male breast cancer incidence rates have remained at a stable low level during for the past four decades. Epidemiologically, MBC occurs continuously with a certain average frequency in the general population and is little affected by environmental factors, but conversely, FBC has a tendency to continuously increase, which may be due to the triggering effect of one or more environmental factors (122). Male breast cancer incidence is generally less than 1 per 100,000 population, in contrast to the much higher incidence of female breast cancer of 122 per 100,000 population (102), i.e. the incidence ratio between MBC and FBC is 0.008, but this ratio is higher among African Americans (123) and is fivefold in Africa, 0.042 (124). While the incidence of MBC generally exhibits a uni-modal distribution, with peak incidence at the age of 71 (50,125), the incidence of FBC tends to have a bimodal distribution (126, 80) with early-onset and late-onset incidence at 52 and 71 years of age (50). Age-specific incidence for men is steadily increasing either constantly (50) or exponentially (62), but increased age-specific incidence for women is rapid up to 50 years of age, but then at a slower pace after menopause (50). Differences in age-specific incidence between men and women reflect differences in underlying risk factors for the disease (102).

But on the other hand, the international correlation between male and female breast cancer incidence rates is quite strong (r = 0.69), meaning that both sexes have several common risk factors for breast cancer (102). Age-specific incidence patterns among men also display a biological similarity between male breast cancer and late-onset female breast cancer (127). This similarity shows that hormonal mechanisms are important (127) but the differences between them may reflect unique mechanisms that may be associated with androgens (18).

Several studies indicate that male breast cancer patients are, on average, 5 to 10 years older than female breast cancer patients at the time of diagnosis (69, 82, 89, 120, 122, 128 -132), but the age gap between men and women is likely to be less in the Middle East and South Asia (5, 133-136). The differences between men and women in the age presentation may also reflect gender differences in underlying risk factors, pathogens, and/or over-diagnosis (102).

In both sexes, a family history of breast cancer can increase the risk of developing this disease (15, 18-22). Genetically, MBC is distinct from FBC (43,137). BRCA1 and BRCA2 mutation genes give an increased risk of breast cancer in both sexes (14, 52, 138) but mutations in these genes do not increase the risk of developing male breast cancer at the same rate in women (139). While mutations in BRCA1 in women can give up to 80% lifetime risk of breast cancer, they do not cause as high a level of risk of breast cancer in men

(128). In women, between 30% and 86% of hereditary breast cancer has been estimated to be aetiologically linked to BRCA1/2 gene mutations, but estimates of these mutations in MBC are significantly smaller (9). Several studies on men with hereditary breast cancer have shown that BRCA1 mutations are significantly less common (26, 27, 37, 42, 140) but many studies show that BRCA2 mutations play a particularly prominent role in the development of breast cancer in men (13, 26, 27, 39, 40, 43, 46, 48, 139-146) BRCA2 mutation also seems to have a stronger role in MBC development than in FBC development in younger people (13, 36). It is also suggested that male breast cancer has a higher genetic than female breast cancer (147).

The relationship between MBC and CBC (contra-lateral breast cancer) is much stronger than the relationship between FBC and CBC i.e. 30 times increased risk of CBC in men, compared to 2-4 times increased risk of CBC in women (28).

Histologically, it is impossible to distinguish between MBC and FBC (14). Almost all the histological breast cancer types described in relation to FBC have also been reported in relation to MBC (12). In both sexes, invasive ductal carcinoma (IDC) is a very common form of breast cancer (8, 65 149-152). But IDC is more common in men than in women (5).

When we look at percentages, non-invasive, in-situ breast cancer in men is not higher than is seen in women before the introduction of mammography screening and it may depend on the size of the male breast, which simplifies the detection of small breast lumps in men using clinical breast examination (63). Papillary breast cancer is relatively more common in men(8,89) i.e. 2% to 4% in men compared with 1% in women (49), but lobular carcinoma is less common in men because of the absence of the mammary glands in the normal male breast (8, 69, 76,78, 81,89-90) Even rarer subtypes of breast cancer, such as medullary, tubular and mucinous types, have been reported in men, although the male equivalent may be somewhat more unusual than the female (6, 63, 64, 81). Inflammatory breast cancer and Paget's disease have been seen with similar levels of frequency in men and women (10, 63). Male breast tumours have a significantly higher frequency of hormone sensitivity, with regard to oestrogen and progesterone, than their female counterparts (85, 103, 107,127, 135, 153-161) which implies a different pathogenesis in the development in of this disease (87). Such differences may play key roles in the therapeutic treatment, which should be grounds for different treatment strategies in comparison with female breast cancer (87).

Older studies show that in contrast to women, the frequency of hormone sensitivity in men does not increase with age (63). But a new study by Giordano et al. (2004) (69) has shown that there is a strong link between this hormone sensitivity in male breast tumours and their age, in the same way that has been observed in women. Oestrogen receptor positivity in males may be a result of the low level of circulating oestrogen in the male body, which is similar to that observed in women after menopause (62). In contrast to this interpretation, several researchers suggest that sexually reducing endocrine condition and/or increased oestrogen production may be the underlying hormonal pattern in MBC cases (162). The amount of testosterone that is converted to oestrogen by aromatase is much greater in men than in women, regardless of a woman's menstrual status, which may explain the differences in approach and response with regard to hormonal treatment of MBC and FBC (163).

HER2-positive breast cancer in men is less common than in women (33, 164-165) which is more correlated with higher cancer stage and with higher histological grade (33). There are several similarities in clinical signs and symptoms of breast cancer in both sexes (73), such as a hard and fixed lump in the breast, with skin or nipple retraction, and nipple discharge and enlarged lymph nodes in the armpit (166). But in MBC, it is more common for the nipple to be affected (76, 131,167) because male breast tumours develop just below the nipple, where rudimentary milk ducts are located, and not in the upper lateral quadrant of the breast, which is characteristic in women (33). Self-detection is the primary form of detection among men, both with cancer in-situ and with invasive breast cancer. However, ductal carcinoma in situ (DCIS) in women is usually detected through screening (168).

Compared to FBC lesions, the edges on MBC lesions are often more defined and calcifications are less frequent and coarser (33, 169), Micro-calcifications occur mainly in ductal carcinoma in-situ (DCIS), which is rarer in men (33,73, 170) Cancer metastases in the lymphatic tissue of the skin are far more common in male breast cancer compared with female breast cancer (136).

Men undergo mastectomy more often than females (171, 172). Men who have undergone mastectomy are more likely than women to receive radiotherapy (95, 168, 173) because of more advanced disease stage and/or more nipple and skin involvement (62). Men are also less likely than women to receive chemotherapy after surgical treatment (173).

FBC prognosis is correlated with patients' age at diagnosis, but conversely, there is no association between age at diagnosis and MBC prognosis. Relative cancer survival in women increases from 35 years of age to age 45-49, and then decreases to the age of 50-59 and then increases again after the age of 65. This means that relative cancer survival in women is a function of age at diagnosis, but relative survival in men has no significant link with age at diagnosis (174).

Compared to women, cancer survival in men is lower, especially in regions where women are routinely

examined with mammography (49). This is because of a more advanced stage of disease at presentation, with higher incidence of lymph node involvement (7, 67, 131) and the low standard of loco-regional treatment for MBC has a significant role for the poorer results (120).

Several studies have shown that survival in MBC patients is almost equal to the survival of FBC patients if the age and stage of disease at diagnosis are matched (50, 69, 83, 161, 175-177), and after adjustment for age at diagnosis, the stage of the disease and the treatment methods, men have actually had significantly better survival from the disease than comparable women (120). A matched analysis of male and female breast cancer patients in a German study by Foerster et al. (2011) (178) has also shown that the 5-year disease-free survival rate was 53.4% (95% CI, range from 54.1 to 66.3%) in men and 62.6%. (95% CI, range from 63.5 to 75.3%) in women, which was not a significant difference ($p > 0.05$), and the 5-year overall survival rate was 71.4% (95% CI, range from 62.1 to 72.7%) in men and 70.3% (95% CI, range from 32.6 to 49.6%) in women, which was also not a significant difference ($p > 0.05$). Xia et al. (2010) (179) have shown in their study that the 5-year and 10-year overall survival rate between Chinese men and women in general are not equal, and that Chinese men have poorer survival rates compared to Chinese women, but when the male group was compared to post-menopausal women, the difference disappeared. In their population-based cohort study, Thalib & Hall (2009) (180) have shown that gender has no significant effect on the prognosis, which was confirmed in a large retrospective study by Hill et al (2005) (181) when 2,923 male breast cancer cases were compared with 442,500 female breast cancer cases. With respect to the variables tumour size, lymph node status, age at diagnosis, histological grading and receptor status, no significant difference has been demonstrated in survival rates for male breast cancer patients compared with female patients in a multivariate analysis in a study by Borgen et al. (1997) (156).

Nahleh et al. (2007) (89) showed in a multivariate analysis that not only tumour size and lymph node status are independent prognostic factors for survival in men, but that gender also serves as an independent prognostic factor. Median survival age between men and women had significant differences when patients have breast cancer at stages I and II, but this difference disappeared at stages III and IV. It was also shown that MBC patients with negative lymph node status had shorter median survival age than FBC patients with the same lymph node status, but this difference also disappeared when both genders had positive lymph node status.

A new study by Ioka et al. (2006) (136) also showed that the 5-year survival rate only decreases with increasing age in men, and that male breast cancer patients have significantly poorer 5-year survival rates compared with women at a corresponding stage of the disease, which is also confirmed in several recent studies (171,182-184) Deaths due to primary breast cancer in men is higher than in women, which is also reported in a study of Gnerlich et al. (2011) (185) and this mortality rate has not changed, unlike female breast cancer (117). It should be emphasised here, the importance of adjuvant systemic therapy, mammography screening, and reduced use of hormone replacement therapy for decreasing mortality among women with breast cancer (127).

The gender difference for prognosis may be a result of anatomical differences between the male and female breast, i.e. undeveloped breast tissue in men facilitates the spread of tumours to the lymphatic tissue in the skin and early regional and distant metastases, both on the overlying skin and on the underlying chest muscle (76) and possibly depends on the biological differences between male and female breast tumours (182, 184) or on a result of the lack of adjuvant systemic therapy (chemotherapy and/or hormonal therapy) (183) or on the effect of co-morbidity and other primary tumours that act as confounding factors (179). With overall survival as a benchmark for comparison, there is no difference between MBC and FBC prognosis in several studies. However, with disease-specific survival as the benchmark for comparison, the same study shows a significant difference between the two groups (176,179).

It is still unclear whether the MBC prognosis is worse than the FBC prognosis, so there is a need for multi-centric prospective studies in this area (177). One should focus on identifying prognostic factors and on defining optimal therapy for MBC patients (173). Psychological differences between male and female patients with breast cancer are also grounds to introduce a different treatment strategy, especially with regard to hormone replacement therapy (117). An early diagnosis with the absence of lymph node involvement has a significant role in improving the outcome of MBC treatment (188).

IV. Conclusion

A significant advance in understanding MBC can improve MBC diagnosis and prognosis. The treatment of MBC has been extrapolated from knowledge available about FBC, although there are many differences in pathogenesis, in biology and in genetics for these two diseases, especially with regard to differences in the role of hormone oestrogen in MBC compared to FBC.

An increased understanding of the potential differences between male and female breast cancer is important, because this can provide new opportunities for therapeutic intervention and probably improved outcomes for MBC treatment. Increased awareness about breast cancer in men will also increase the

chances of early detection and result in improved prognosis. Clearer treatment guidelines are also necessary in order to improve MBC prognosis. Increased input is needed for informative and psychological support for MBC patients and public education should be oriented toward men at higher risk to reduce symptom duration before diagnosis.

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