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REVIEW

Understanding and management of male breast cancer: a critical review

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Abstract Breast cancer is a rare disease in men representing nearly 1% of the total breast cancer cases worldwide. While treatments developed for women with breast cancer are often applied to treat men with breast cancer, however, lack of awareness of this disease leads to its detection at a later stage in men. This review discusses male breast cancer and draws comparisons with female breast cancer and discusses current treatments available to treat this disease. It is believed that this review shall provide concise and relevant information increasing the awareness of issues revolving around male breast cancer (MBC).

Keywords Male breast cancer

Introduction

Breast cancer in men (male breast cancer, MBC) is an uncommon disease [1, 2]. Nearly 2,030 new cases of male breast cancer will be diagnosed in the year 2007 out of a total of 180,510 breast cancer cases (American Cancer Society statistics). While this number represents only 1.12% of all breast cancer cases, it is, however, important to note that the number of cases of MBC have gone up from 1,400 (out of 181,600 cases of breast cancer diagnosed) in 1997 to 2,030 in 2007. This represents a nearly 45% increase in the number of cases of MBC. Table 1 shows the relative numbers of male and female breast cancer cases and deaths over the past decades.

Due to great advances made in the detection and treatments of female breast cancer (FBC), there exist several therapies and detection methods that have been applied to study, detect and treat MBC [3, 4]. However, there exists a severe lack of awareness even among the educated members of society about MBC. Breast cancer is often wrongly considered a woman's disease and with a dramatic increase in the number of cases of MBC it is essential that this disease be studied in greater detail. While most treatments of FBC are often extrapolated to MBC, it is however important to realize the inherent differences between these two diseases. Further, only a few studies exist that distinguish between male and female breast cancers at a molecular and cellular level [2, 5]. The situation is further complicated by the lack of any commercially available cell lines to study MBC.

In this article we discuss the similarities and differences between breast cancer in men and women, the etiology of the disease, the respective treatments and the psychological impact on the patients.

Key differences in male and female breast cancers

Table 2 summarizes some of the important differences between male and female breast cancers. They both exhibit similar range of morphological diversity and histological classification. The majority of MBC's are classified on histological grounds as infiltrating ductal carcinoma [6]. However, due to the absence of lobules and acini in men, around 1% of all MBC's are lobular in nature as compared to over 10% in females [7, 8]. The average age of men diagnosed with breast cancer is about 5–10 years greater

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Table 1 Number of Female breast cancer (FBC) and Male breast cancer (MBC) cases and deaths in the last decade

Year	FBC cases	FBC deaths	MBC cases	MBC deaths
1997	180,200	43,900	1,400	290
1998	178,700	43,500	1,600	400
1999	175,000	43,300	1,300	400
2000	182,800	41,200	1,400	400
2001	192,200	40,200	1,500	400
2002	203,500	39,600	1,500	400
2003	211,300	40,200	1,300	400
2004	215,990	40,110	1,450	470
2005	211,240	40,410	1,690	460
2006	212,920	40,970	1,720	460
2007	178,480	40,460	2,030	450

Data obtained from American Cancer Society's cancer statistics

than women diagnosed with breast cancer. Also, men are more likely to have estrogen and progesterone receptor positive breast cancers. Men with BRCA2 mutations are more likely to possess a higher risk of developing breast cancer as are men with Klinefelter's syndrome [7–11]. Studies so far performed have not shown any clear trends in relative expression of oncogenes such as Her2, bcl2, and p53 [12]. However, statistics collected over the time clearly shows that MBC patients are more likely to be diagnosed at an advanced stage of the disease having metastasized to the lymph nodes and tumor size larger than 1 cm in diameter [7, 8].

Sources of estrogen in men and women

A much greater percentage of breast cancers in men compared to women are likely to be estrogen receptor positive, therefore it is necessary to summarize the sources of estrogen and related hormones in men and women and how these differences are likely to affect men with breast cancer. In pre-menopausal women, the primary sources of estrogen are ovaries (0.37 nmol/l of estradiol in serum) [13]. However, in postmenopausal women there is a dramatic reduction in estrogen production and the amounts of circulating estrogen in the plasma is lower than the amount in men (0.04 nmol/l of estradiol in postmenopausal women compared to 0.1 nmol/l in men) [14]. Further, the amount of testosterone in men is at least 20 times more than that in postmenopausal women (0.6 nmol/l in women compared to 12 nmol/l in men). These increased hormonal levels have been known to contribute towards a greater proliferation of breast cancer [14].

The importance of the role played by locally produced estrogen in MBC, has increasingly been realized in recent years. There are several extragonadal sites of estrogen production, such as mesenchymal cells of the adipose tissue or skin, osteoblasts in the bone, vascular endothelial and aortic smooth muscle cells, medial preoptic/anterior/basal hypothalamus, and the amygdala. In addition to these, in men the leydig cells and other cells of the testes including germ cells produce estrogen [15–20]. The testes are thought to account for 15% of circulating estrogen in men. An important difference in the estrogen production between ovaries and the extragonadal sites is that the extragonadal sites are dependent on the circulating precursor C19 steroids for estrogen biosynthesis unlike the ovaries which can also synthesize the C19 precursors [21–23]. The conversion of steroidal androgens (testosterone and androstenedione) to estrogens (estradiol and estrone) is carried out by a Cytochrome P450 type enzyme called aromatase which is encoded by the CYP19 gene. This gene is regulated differently in various tissues. In ovaries the CYP19 is regulated by the follicle stimulating hormone, in the placenta it is regulated by the distal promoter I.1 and in the bones and tissue the distal promoter I.4 drives *CYP19* expression [18, 20].

Studies in cases of female breast cancer have shown the role of estrogen in promoting breast cancer, with women

Table 2 Key similarities and differences between male and female breast cancer [7]

Property	Male	Female
Median age	67	62
Genetic mutations linked to higher cancer risk	BRCA2	BRCA1 and BRCA2
% of Estrogen receptor positive breast cancers	90	76
% of Progesterone receptor positive breast cancers	85	67
% of patients diagnosed with tumor size < 1 cm	9.8	20
% of lymph node positive cancers	32.1	22.7
% of cancers diagnosed at stage 0	10.5	14.4
% of cancers diagnosed at stage 1	29.4	38.4
% of cancers diagnosed at stage 2	38.5	28.4
% of cancers diagnosed at stage 3	7.5	5.3
% of cancers diagnosed at stage 4	5.7	3.9

treated with hormone replacement therapy (HRT) likely to have a 1.35-fold higher chance of developing breast cancer (Collaborative Group on Hormonal Factors in Breast Cancer 1997)[15]. Further, the concentration of estradiol in breast cancer patients has been observed to be 20-fold greater in breast tumors compared to that present in plasma. The evidence that aromatase inhibitor treatment results in a decline in estrogen concentration and aromatase activity suggests that the surrounding breast adipose tissue is responsible for the high concentrations of estrogen [15, 24]. Further, the ability of the bone osteoblasts to produce estrogen also make them a target for the metastasis of breast cancer [14, 15]. Therefore, the role of estrogen in promoting the growth and proliferation in women is well documented. In men, due to much lower mass of adipose tissue in the breast, the local estrogen production is much lower, probably leading to lower incidence of breast cancer in men. However, the primary constituents necessary for their conversion to estrogen, such as precursors for estrogen production (testosterone and androstenedione) are present in higher concentrations. It is only the lack of adipose tissue related aromatase that prevents the conversion of these C19 steroids into estrogen [14]. However, the increasing obesity rates across the globe are likely to increase the amount of aromatase thereby significantly raising levels of estrogen. While no studies are available linking obesity and estrogen production or breast cancer in men, there is a very real possibility that changing lifestyles might lead to greater incidence of breast cancer in men.

Treatments for male breast cancer

All treatments for male breast cancer are extrapolated from experience in cases of female breast cancer. There are no treatments that target breast cancer in men, specifically. Although most treatments are similar, we discuss the differences in hormonal therapies in greater detail due to differences in the levels of hormones between males and females.

Surgery

Radical, simple, and modified mastectomy have been used to treat MBC. Radical mastectomy has been used against larger tumors and it almost always involves the skin and muscle. In invasive MBC cases, axillary dissection is performed. Since axillary dissection has side effects such as shoulder pain, arm pain, loss of sensitivity and arm oedema, there have been cases where sentinel node biopsy has been used. The European Institute of Oncology at Milan has proposed the use of this technique in patients with tumor size less than 2.5 cm and without clinical evidence of axillary node involvement (ANI) [25–28].

Radiotherapy

Many studies have asserted the need for adjuvant loco regional irradiation (RT or radiotherapy) in MBC [26, 29, 30]. The European Institute of Oncology has proposed RT in case of tumors that are greater than 1 cm in diameter or with more than one metastatic lymph node [26]. It is strongly recommended after radical or modified mastectomy and axillary dissection analogous to similar treatments in postmenopausal women. In a recent France Cancer Center study, out of 690 patients evaluated, 490 underwent postoperative RT. The Chest wall and supraclavicular fossa were treated in 85 and 75% of the patients, respectively. Intermammary chain and axillary were treated in 77 and 51% of the cases, respectively. Local recurrence occurred in 9.5% of the cases (among 7.3 and 13.0% of the patients with and without RT) [26].

Adjuvant hormonal treatment

Since, an overwhelming number of cases of MBC (approximately 90%) are ER-positive, Tamoxifen is used as the standard adjuvant therapy. No large-scale randomized clinical trials have been performed to study the effects of adjuvant tamoxifen treatment on the disease free survival (DFS) or overall survival (OS) rates in MBC although many smaller studies have been performed. In a study published in 1999 by Goss et al. [25] the results of treatments for 229 MBC patients over 40 years were described. Notably, 57 patients were subjected to adjuvant hormonal therapy and this was shown to improve DFS and OS. Another analysis of 301 cases treated in the Christie Hospital and Holt Radium Institute at Manchester showed an increased survival (55%) among patients who were administered adjuvant Tamoxifen for a year following surgery and radiotherapy compared to those who were not administered to adjuvant Tamoxifen (28%) [31].

In a separate study by Giordano et al. [7] at the M.D. Anderson Cancer Center at Houston, data reviewed from 135 men diagnosed with non-metastatic breast cancer between 1994 and 2001 was published. Out of these, 38 men received adjuvant hormonal therapies (19 adjuvant hormonal therapy only and 19 adjuvant hormonal + adjuvant chemotherapy, 35 of them on tamoxifen). The Kaplan–Meier curves of time to recurrence and overall survival of patients plotted clearly revealed better survival for patients exposed to adjuvant hormonal therapy with hazards ratio of for time to recurrence being 0.49 and 0.45

for survival (both at 95% confidence interval) respectively, compared with those who did not receive hormonal therapy. Side effects observed in adjuvant tamoxifen treatments have been hot flushes, weight gain, depression, impotence, and thromboembolic accidents.

Aromatase inhibitors (AI's) have not been used extensively to treat MBC and trials performed so far, have been on a very small number of patients with no clear results [32, 33]. It has been proposed that use of AI's increases the amount of testosterone in men which only increases the androgen available for conversion to estrogen at a later stage or lead to other side effects [30, 34]. On the other hand, it has been proposed that combining AI's with drugs to suppress testicular estrogen as well as suppress production of androgens (leuprolide acetate, goserelin) is likely to have a better response. A combination of different drugs would ideally be most suited to create an effective drug regimen where adjuvant hormonal therapy is effective in MBC [30]. However due to a much lesser number of patients and availability of a few scattered studies, an elaborate and clear drug regimen is difficult to develop against MBC. Currently the Southwest Oncology group of the National Cancer Institutes in the USA is recruiting 56 patients for a phase II study to evaluate the efficacy of anastrazole in combination with goserelin acetate in ER positive MBC (www.cancer.gov/clinicaltrials/SWOG-SO511).

Adjuvant chemotherapy

The benefits of adjuvant chemotherapy are not well established. Further, since over 30% of the cases of MBC are in patients over 70 years of age, problems related to toxicity are high in these cases [35]. Chemotherapy regimes include cyclophosphamide-methotrexate-5-fluoracil (CMF) or anthracycline-based regimens (primarily 5-fluoracil-adriamycin-cyclophosphamide (FAC)), although taxanes have been used in adjuvant setting [36]. In a study on 24 patients with stage II disease treated with CMF, the projected 5 year survival rate was 80% (95% confidence interval 74–100%) while a study on 11 patients with stage II or III disease who were treated with FAC, there was a 63% disease free survival rate and a 91% survival rate in 4.25 years [30, 37–39]. The Early Breast Cancer Trialist Collaborative Group (EBCTCG) recommends adjuvant chemotherapy on patients less than 70 years of age, axillary node involvement and estrogen receptor negative cancer [40].

Support for men with breast cancer

The popular perception of breast cancer as being a woman's disease leaves many men perplexed and surprised when diagnosed with breast cancer. A recent study on the psychological effects of breast cancer on men suffering from MBC concluded that most men were surprised on being diagnosed by what they had thought was a woman's disease and often wished it was called something else. The men further felt that there was not enough information oriented for men as most handouts and leaflets dealt with the problems from a women's perspective and there were no support groups for men to discuss their problems. The lack of awareness on breast cancer causes further distress when patients diagnosed with it try to talk about it with friends and peers, where the reaction is one of disbelief, and sadly often one of amusement [5, 41–43].

Conclusions

Raising awareness about MBC could save many lives. Once men realize that they too could get breast cancer they are more likely to talk to their doctors about it when they observe a lump or related symptoms. As Table 2 shows, the disease is diagnosed in men at a later stage than women. One reason is ignorance about the disease. Further it is likely that men suffering from this disease shall feel free to mention it and discuss it with friends and peers if the awareness of this disease is high.

Another problem is the small number of patients scattered round the world hinders any effective and large scale clinical trials. The only possibility of large-scale clinical trials being conducted is through organizing international collaborations involving countries not only in Europe and North America, but also in Asia and Africa. Only by such an international cooperation can useful epidemiological data be gathered and effective clinical trials performed to effectively develop a drug regimen to treat male breast cancer.

References

1. Ravandi-Kashani F, Hayes TG. Male breast cancer: a review of the literature. Eur J Cancer 1998;34:1341–7.
2. Giordano Sharon H, Buzdar Aman U, Hortobagyi Gabriel N. Breast cancer in men. Ann Intern Med 2002;137:678–87.
3. Arnould N, Pouget O, Gharbi M, Brettes JP. Breast cancer in men: are there similarities with breast cancer in women? Gynecol Obstet Fertil 2006;34:413–9.
4. Giordano Sharon H. A review of the diagnosis and management of male breast cancer. Oncologist 2005;10:471–9.
5. Iredale R, Brain K, Williams B, France E, Gray J. The experiences of men with breast cancer in the United Kingdom. Eur J Cancer 2006;42:334–41.
6. Jonasson JG, Agnarsson BA, Thorlacius S, Eyfjord JE, Tulinius H. Male breast cancer in Iceland. Int J Cancer 1996;65:446–9.
7. Giordano Sharon H, Cohen Deborah S, Buzdar Aman U, Perkins G, Hortobagyi Gabriel N. Breast carcinoma in men: a population-based study. Cancer 2004;101:51–7.

8. Joshi MG, Lee AKC, Loda M, et al. Male breast carcinoma: an evaluation of prognostic factors contributing to a poorer outcome. Cancer 1996;77:490–8.
9. Stratton MR, Ford D, Neuhasen S, et al. Familial male breast cancer is not linked to the BRCA1 locus on chromosome 17q. Nat Genet 1994;7:103–7.
10. Karhu R, Laurila E, Kallioniemi A, Syrjakoski K. Large genomic BRCA2 rearrangements and male breast cancer. Cancer Detect Prev 2006;30:530–4.
11. Thompson D, Easton D. Variation in cancer risks, by mutation position, in BRCA2 mutation carriers. Am J Hum Genet 2001;68:410–9.
12. Chakrabarti J, Rampaul RS, Guevara C, et al. The pathology of male breast cancer. Int J Cancer Prev 2005;2:213–23.
13. Gann PH, Geiger AS, Helenowski IB, Vonesh EF, Chatterton RT. Estrogen and progesterone levels in nipple aspirate fluid of healthy premenopausal women: relationship to steroid precursors and response proteins. Cancer Epidemiol Biomarkers Prev 2006; 15:39–44.
14. Simpson ER. Sources of estrogen and their importance. J Steroid Biochem Mol Biol 2003;86:225–30.
15. Simpson E, Rubin G, Clyne C, et al. Local estrogen biosynthesis in males and females. Endocr Relat Cancer 1999;6:131–7.
16. Shozu M, Simpson ER. Aromatase expression of human osteoblast-like cells. Mol Cell Endocrinol 1998;139:117–29.
17. Shozu M, Zhao Y, Simpson ER. Estrogen biosynthesis in THP1 cells is regulated by promoter switching of the aromatase (CYP19) gene. Endocrinology 1997;138:5125–35.
18. Simpson ER, Zhao Y, Agarwal VR, et al. Aromatase expression in health and disease. Recent Prog Horm Res 1997;52:185–213;discussion 213–4.
19. Agarwal VR, Ashanullah CI, Simpson ER, Bulun SE. Alternatively spliced transcripts of the aromatase cytochrome P450 (CYP19) gene in adipose tissue of women. J Clin Endocrinol Metab 1997;82:70–4.
20. Zhao Y, Agarwal VR, Mendelson CR, Simpson ER. Estrogen biosynthesis proximal to a breast tumor is stimulated by PGE2 via cyclic AMP, leading to activation of promoter II of the CYP19 (aromatase) gene. Endocrinology 1996;137: 5739–42.
21. Tsai-Morris CH, Aquilano DR, Dufau ML. Cellular localization of rat testicular aromatase activity during development. Endocrinology 1985;116:38–46.
22. Nitta H, Bunick D, Hess RA, et al. Germ cells of the mouse testis express P450 aromatase. Endocrinology 1993;132:1396–401.
23. Hemsell DL, Grodin JM, Brenner PF, Siiteri PK, MacDonald PC. Plasma precursors of estrogen II. Correlation of the extent of conversion of plasma androstenedione to estrone with age. J Clin Endocrinol Metab 1974;38:476–9.
24. de Jong PC, van de Ven J, Nortier HW, et al. Inhibition of breast cancer tissue aromatase activity and estrogen concentrations by the third-generation aromatase inhibitor vorozole. Cancer Res 1997;57:2109–11.
25. Goss PE, Reid C, Pintilie M, Lim R, Miller N. Male breast carcinoma: a review of 229 patients who presented to the Princess Margaret Hospital during 40 years: 1955–1996. Cancer 1999;85: 629–39.
26. Cutuli B. Strategies in treating male breast cancer. Expert Opin Pharmacother 2007;8:193–202.
27. Cutuli B, Lacroze M, Dilhuydy JM, et al. Male breast cancer: results of the treatments and prognostic factors in 397 cases. Eur J Cancer 1995;31A:1960–4.
28. Gennari R, Curigliano G, Jereczek-Fossa Barbara A, et al. Male breast cancer: a special therapeutic problem. Anything new? Int J Oncol 2004;24:663–70.
29. Ben Dhiab T, Bouzid T, Gamoudi A, et al. Male breast cancer: about 123 cases collected at the Institute Salah-Azaiz of Tunis from 1979 to 1999. Bull Cancer 2005;92:281–5.
30. Agrawal A, Ayantunde AA, Rampaul R, Robertson JFR. Male breast cancer: a review of clinical management. Breast Cancer Res Treat 2007;103:11–21.
31. Ribiero G. Male breast carcinoma: a review of 301 cases from the Christie Hospital and Holt Radium Institute, Manchester. Br J Cancer 1985;51:115–9.
32. Nahleh ZA. Hormonal therapy for male breast cancer: a different approach for a different disease. Cancer Treat Rev 2006;32:101–5.
33. Dutta U, Pant K. Aromatase inhibitors: past, present and future in breast cancer therapy. Med Oncol 2007. doi:10.1007/s12032-007-9019-x.
34. Turner KJ, Morley M, Atanassova N, Swanston ID, Sharpe RM. Effect of chronic administration of an aromatase inhibitor to adult male rats on pituitary and testicular function and fertility. J Endocrinol 2000;164:225–38.
35. Giordano Sharon H, Duan Z, Kuo Y-F, Hortobagyi Gabriel N, Goodwin James S. Use and outcomes of adjuvant chemotherapy in older women with breast cancer. J Clin Oncol 2006;24:2750–6.
36. Giordano Sharon H, Perkins George H, Broglio K, et al. Adjuvant systemic therapy for male breast carcinoma. Cancer 2005;104: 2359–64.
37. Fentiman Ian S, Fourquet A, Hortobagyi Gabriel N. Male breast cancer. Lancet 2006;367:595–604.
38. Bagley CS, Wesley MN, Young RC, Lippman ME. Adjuvant chemotherapy in males with cancer of the breast. Am J Clin Oncol 1987;10:55–60.
39. Patel HZ II, Buzdar AU, Hortobagyi GN. Role of adjuvant chemotherapy in male breast cancer. Cancer 1989;64:1583–5.
40. Early Breast Cancer Trialists' Collaborative Group. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomized trials. Lancet 2005;365:1687–717.
41. Kiss A, Meryn S. Effect of sex and gender on psychosocial aspects of prostate and breast cancer. BMJ 2001;323:1055–8.
42. Moynihan C. Theories in health care and research: theories of masculinity. BMJ 1998;317:1072–5.
43. Lee C, Owens RG. Issues for psychology of men's health. J Health Psychol 2002;7:209–17.