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Review

The biology of male breast cancer

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ABSTRACT

Important differences have begun to emerge concerning the molecular profile of female and male breast cancer which may prove to be of therapeutic value. This review examined all the available data on the genomics of MBC. Most male cancers are ER+ve but without a corresponding increase in PR positivity and only a weaker association with estrogen-controlled markers such as PS2, HSP27 and Cathepsin-D. HER2 +ve cancers are rare in males and the role of androgen receptor is controversial. Although the Luminal A phenotype was the most frequent in both MBC and FBC, no Luminal B or HER2 phenotypes were found in males and the basal phenotype was very rare. Using hierarchical clustering in FBC, ERα clustered with PR, whereas in MBC, ERα associated with ERβ and AR. Based on limited data it appears that Oncotype DX is effective in determining recurrence risk in selected MBC. In future, tailored therapies based on genomics will probably yield the most promising approach for both MBC and FBC.

Contents

1. Introduction

There have been multiple well-meaning attempts to show that, after adjusting for stage and age, the prognosis of male breast cancer (MBC) is similar to that of female breast cancer (FBC). This approach misses the essential gender differences in the diseases having non-congruent molecular characteristics which are potentially exploitable [1]. Striking differences are observed in the expression of hormone receptors, HER2, Ki67 and BCL2. Additionally the molecular signatures of MBC and FBC are markedly different. These findings will be analysed in relation to prognosis and selection of systemic therapy.

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2. Estrogen and progesterone receptor (ER, PR)

Two large series of ER status in MBC with have been reported. In the French MBC series ER positivity was reported in 385/419 (92%) and 356/399 (89%) were PR positive [2]. Among the MBC tumours the receptor phenotype was: ER+ve PR+ve (86%), ER+ve PR−ve (6%), ER−ve PR+ve (3%) and ER−ve PR−ve (5%). Chavez-Macgregor et al. analysed 829 MBC from the California Cancer Registry and of these receptor data was available on 606 [3]. Overall, 494 (82%) were hormone receptor positive and this percentage increased with age being 67% in those <50years compared with 83% in males aged ≥70 years (p = .002). In terms of ethnicity, of the non-Hispanic white men, tumours were ER+ve in 83% compared with 73% of those in non-Hispanic blacks.

Weber-Chappuis et al. measured ER/PR status in 66 MBC and 190 FBC specimens and found higher rates of receptor positivity in males [4]. Paradoxically, in ER+ve males there was a weaker association with estrogen-controlled markers such as PS2, HSP27, Cathepsin-D and even PR. Curigliano et al. analysed both ER and PR together with the kinase inhibitor proteins (KIPs) p27Kip1 and p21Waf1 and reported that there was increased immunoreactivity for all four in MBC [5]. In a population-based from Saskatchewan Cancer Foundation Muir et al. found a greater frequency of ER positivity in males but no significant difference in PR status of males and females [6]. In the largest study, Shaaban et al. immunostained tissue microarrays of tumours from 251 MBC and 263 FBC [7]. They confirmed the higher incidence of ER positivity in MBC compared with FBC but found no difference in PR expression.

Shandiz et al. examined receptor status in 17 MBC and 338 FBC treated in Iran [8]. Among the males the tumours were ER+ve in 82% compared with 53% in females (p = .016). Again there was no significant difference in PR positivity (59% versus 50%). When ER status in MBC was compared with that of post-menopausal women it was more frequently positive (82% against 49%, p = .010). In a recent meta-analysis of 1984 MBC tumours, Humphries et al. reported that >80% were ER+ve and >70% PR+ve[9]. The comparative studies are summarised in Table 1.

3. Androgen receptor (AR)

Immunoreactivity for AR is positive in 38–81% of MBC tumours [7,10,11]. This broad range may be hiding important functional differences in the AR gene. Androgens have been deemed to be protective in terms of MBC and a mutated AR gene within the region encoding the DNA binding domain on the X chromosome is responsible for Reifenstein syndrome with androgen resistance and predisposition to MBC [12]. Chamberlain et al. constructed ARs with varying position and length of the polyglutamine tract, and showed that elimination of the tract in human AR caused elevation of transcriptional activation indicating that its presence was inhibitory [13]. Conversely, expansion of the CAG repeat in AR was associated with a linear decrease in transactivation. In 2 large studies comprising 251 and 1986 cases of MBC, among those with ER+ve cancers the presence of AR was a marker of better prognosis[7 9].

Table 1
Studies comparing ER/PR status in MBC and FBC.

Author	MBC	FBC
Weber-Chappuis 1996 [4]	N = 66	N = 190
ER+ve	54 (82%)	142 (75%)
PR+ve	51 (77%)	116 (62%)
Curigliano 2002 [5]	N = 27	N = 101
ER+ve	27 (100%)	63 (64%)
PR+ve	26 (96%)	38 (38%)
Muir 2003 [6]	N = 75	N = 240
ER+ve	61 (81%)	166 (69%)
PR+ve	47 (63%)	134 (56%)
Shaaban 2012 [7]	N = 251	N = 263
ER+ve	201 (80%)	180 (68%)
PR+ve	177 (71%)	190 (72%)
Shandiz 2015 [8]	N = 17	N = 338
ER+ve	14 (82%)	179 (53%)
PR+ve	10 (59%)	168 (50%)

4. HER2

HER2 (neu) is a transmembrane receptor protein which is overexpressed in approximately 35% of FBC and is associated with a significantly worse prognosis [14]. Bloom et al. carried out immunohistochemistry (IHC) and fluorescence in situ hybridisation (FISH) on paraffin −fixed specimens from 58 MBC and 202 FBC to compare HER2 expression by gender [15]. The surprising result was that only 1 (1.7%) of the MBC tumours showed +++ staining of HER-2 and none had HER2 gene amplification. Among the FBC specimens there was expression on HER2 in 52 (26%) and gene amplification in 55 (27%). In the Shaaban study none of the MBC specimens expressed HER2 compared with 5 (2%) of the FBC tumours [7]. In the meta-analysis of Humphries et al. [9], HER2 expression was similarly uncommon apart from one study which showed 18/41 cases were HER2 positive [16].

5. Molecular profile

Sorlie et al. investigated 115 breast cancers from females to determine the expression of 534 intrinsic genes by hierarchical clustering [17]. They found 4 major groups: luminal A (43%), luminal B (20%), HER2 (10%) and basal (46%). When male cancers were analysed the results were very different. Using immunohistochemuistry and hierarchical clustering Shaaban et al. assayed tumours from 251 MBC and as controls 263 FBC, matched for tumour grade, patient age, and nodal status [7]. Although the Luminal A was the most frequent phenotype in both MBC and FBC, there were no Luminal B or HER2 phenotypes in males and basal phenotype was rare in both. Hierarchical clustering demonstrated that whereas in females estrogen receptor alpha (ERα) clustered with progesterone receptor (PR), the situation in males was that ERα associated with estrogen receptor beta (ERβ) and androgen receptor (AR).

As a different and simpler approach Kornegor et al. carried out immunohistochemistry (IHC) for ER, PR, HER2, EGFR, CK5/6, CK14 and Ki67 on samples from 134 MBC cases [18]. Of these 75% proved to be luminal A, 21% luminal B and the remainder were either basal type (4) or unclassifiable triple negative (1). Nilsson et al. examined tumours from 197 MBC cases using both IHC on tissue microarrays and tumour grading from conventional slides [19]. The majority were both ER positive (93%) and PR positive (77%) with HER2 positivity in only 11%. Of the cancers, 82% were luminal A and 11% luminal B with only 2 basal-like cancer and no HER2-like tumours. In contrast to FBC breast cancer mortality in the luminal subgroups was similar.

Shildhaus et al. used IHC on 96 MBC specimens to look for CEP17, HER2 and Topo II-α alterations by together with ER/PR, HER2 and Ki67 [20]. They found both HER2 and Topo II-α amplification/deletions were very uncommon so that anthracycline sensitivity linked to HER2/Topo II-α alterations was of minimal significance in MBC. Abreu et al. used an IHC panel of ER, PR. AR, HER2, ki67 and p53 on 111 MBC and used hierarchical clustering to delineate subgroups [21]. Most (89%) were luminal A, 7% B, and only 4% basal and <1% HER2 enriched. In multivariate analysis factors predicting poor prognostic outcome on operable disease were size >2 cm and ER negativity. The combined MBC results of these series are