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Review

Molecular profiling of male breast cancer – Lost in translation?☆

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ABSTRACT

Breast cancer is the most common cancer form in women and it has been extensively studied on the molecular level. Male breast cancer (MBC), on the other hand, is rare and has not been thoroughly investigated in terms of transcriptional profiles or genomic aberrations. Most of our understanding of MBC has therefore been extrapolated from knowledge of female breast cancer. Although differences in addition to similarities with female breast cancer have been reported, the same prognostic and predictive markers are used to determine optimal management strategies for both men and women diagnosed with breast cancer. This review is focused on prognosis for MBC patients, prognostic and predictive factors and molecular subgrouping; comparisons are made with female breast cancer. Information was collected from relevant literature on both male and female breast cancer from the MEDLINE database between 1992 and 2014.

MBC is a heterogeneous disease, and on the molecular level many differences compared to female breast cancer have recently been revealed. Two distinct subgroups of MBC, luminal M1 and luminal M2, have been identified which differ from the well-established intrinsic subtypes of breast cancer in women. These novel subgroups of breast cancer therefore appear unique to MBC. Furthermore, several studies report inferior survival for men diagnosed with breast cancer compared to women. New promising prognostic biomarkers for MBC (*e.g.* NAT1) deserving further attention are reviewed. Further prospective studies aimed at validating the novel subgroups and recently proposed biomarkers for MBC are warranted to provide the basis for optimal patient management in this era of personalized medicine.

This article is part of a Directed Issue entitled: Rare Cancers.

Contents

Abbreviations: aCGH, array based comparative genomic hybridization; BCSS, breast cancer specific survival; DFS, disease free survival; EMT, epithelial-mesenchymal transition; EORTC, European Organization for Research and Treatment of Cancer; ER, estrogen receptor; IHC, immunohistochemistry; MBC, male breast cancer; NHG, Nottingham histological grade; OS, overall survival; PR, progesterone receptor; TCGA, The Cancer Genome Atlas; TMA, tissue microarray.

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1. Introduction

Male breast cancer (MBC) is similar to breast cancer in women in some aspects; for instance invasive ductal carcinoma is the most common histological type (Fentiman et al., 2006; Korde et al., 2010), and it is often detected as a painless subareolar lump and may also involve nipple retraction or bleeding from the nipple (Giordano, 2005; Ruddy and Winer, 2013). However, there are also many differences between breast cancers occurring in men *vs.* women. Most notably, breast cancer is much less common in men (only 1% of all breast cancers in the US (Siegel et al., 2013) and 0.5% in the Nordic countries (Engholm et al., 2013) occur in men), men are often older at diagnosis (67 *vs.* 62 years) (Giordano et al., 2002), their tumors are more often hormone receptor positive (estrogen receptor (ER) positivity 91–95% *vs.* 76–78% and progesterone receptor (PR) positivity 80–81% *vs.* 67%, in men and women, respectively) (Anderson et al., 2010; Giordano et al., 2002; Nilsson et al., 2013b). Lobular carcinoma is also much less common in men (Giordano et al., 2002; Weigelt et al., 2010).

A family history of breast and ovarian cancer is a risk factor for developing breast cancer in men, as in women; germline *BRCA2* mutations have been reported in 4–14% of MBC patients, while *BRCA1* mutations are less frequent, occurring in up to 4% of MBC patients (Basham et al., 2001; Chodick et al., 2008; Couch et al., 1996; Ding et al., 2010; Friedman et al., 1997; Ottini et al., 2008; Struewing et al., 1999). *BRCA1* and *BRCA2* mutations confer an estimated increased lifetime risk of developing breast cancer of 1–6% and ~7%, respectively (Levy-Lahad and Friedman, 2007; Liede et al., 2004; Tai et al., 2007), while the general lifetime risk in the male population is 0.1% (Engholm et al., 2013; Liede et al., 2004). Among other germline mutations that confer a moderately increased risk of developing breast cancer in women, data for men are mixed for *PALB2*, *CHEK2* and *CYP17* (Blanco et al., 2011; Ding et al., 2010; Falchetti et al., 2007; kConFab et al., 2009; Ohayon et al., 2004; Silvestri et al., 2010b; Syrjäkoski et al., 2003; Wasielewski et al., 2008; Young et al., 1999), while no increased risks have been found for *BRIP1* and *RAD51 C* with regards to MBC (Silvestri et al., 2010a, 2011). A large genome-wide association study of MBC has identified *TOX3* and *RAD51B* to confer increased risks for MBC, the *RAD51B* locus being a novel breast cancer susceptibility locus (Orr et al., 2012). Other risk factors for men are associated with changes in the hormonal balance of estrogen to androgen, such as in Klinefelter's syndrome (resulting in a 50-fold increased risk) (Brinton et al., 2009; Hultborn et al., 1997), testicular abnormalities that result in testosterone deficiency (Brinton et al., 2009; Thomas et al., 1992), liver diseases (Sørensen et al., 1998), obesity (Brinton et al., 2008, 2009; Ewertz et al., 2001; Hsing et al., 1998) and exogenous estrogen exposure (Medras et al., 2006; Thellenberg et al., 2003).

The number of breast cancer diagnoses among women has increased over the past decades (Ly et al., 2012; Socialstyrelsen, 2012), while the incidence of MBC has not risen in most countries (Ly et al., 2012), with the exception of a slight increase that has been reported from England, Scotland, Australia and the USA (Giordano et al., 2004; Speirs and Shaaban, 2008; Stang and Thomssen, 2008; White et al., 2011).

Research into the etiology and tumor biological properties of MBC has been limited due to the rareness of the disease, and most data are derived from retrospective studies covering long time periods and geographical regions. Therefore, MBC patients are currently being managed according to guidelines developed for female patients; there is however currently insufficient knowledge to determine whether this is the most optimal strategy.

2. Prognosis of male breast cancer

The outcome of men diagnosed with breast cancer compared to women is currently debated. Many recent studies have shown worse survival for MBC patients (Chen et al., 2013; Gnerlich et al., 2012; Greif et al., 2012; Miao et al., 2011; Nilsson et al., 2011; Scott-Conner et al., 1999; Yildirim and Berberoğlu, 1998); however this difference becomes less apparent when the cohorts are stratified on various prognostic factors (Giordano et al., 2004; Miao et al., 2011; Shaaban et al., 2012). Table 1 summarizes the largest studies comparing survival for male and female breast cancer patients to date (Chen et al., 2013; Giordano et al., 2004; Gnerlich et al., 2012; Greif et al., 2012; Miao et al., 2011; Nilsson et al., 2011; Scott-Conner et al., 1999; Shaaban et al., 2012).

Many of the studies in Table 1 cover long periods of time, are based on small sample sizes, and/or include patients from many different hospitals and sometimes also countries. This is an unavoidable consequence of the rarity of the disease and limits the interpretation of the results. Moreover, when comparing overall survival (OS) between the genders, it needs to be taken into consideration that women have a slightly longer expected survival than men; *e.g.* in Sweden, life expectancy is 84 years for women and 80 years for men (Centralbyrån, 2014). Nevertheless, Table 1 includes two single center studies: one from Sweden including 99 MBC patients and one from China with 150 MBC patients, and both these studies showed inferior outcome for MBC patients (Chen et al., 2013; Nilsson et al., 2011). The Swedish study matched on age and date of diagnosis, and contrary to what has been anticipated from the literature, found no differences in disease stage between the genders. Despite this, a significantly worse relative survival was observed for men (Nilsson et al., 2011). The Chinese study matched patients for age, date of diagnosis and stage, and found a significantly inferior disease-free as well as OS for men (Chen et al., 2013). We know today that breast cancer is a very heterogeneous disease in general and that it can be divided into comprehensive subgroups associated with differences in response to treatment and outcome. The question therefore arises on which factors one should match when comparing outcome for men *vs.* women diagnosed with breast cancer. Notwithstanding, when male and female breast cancer patients are compared on a population based level, the relative overall and breast cancer specific survival appears to be worse for male patients (Cancerfonden, 2013; Chen et al., 2013; Greif et al., 2012; Miao et al., 2011; Nilsson et al., 2011). For example, in Sweden the relative 5-year OS rates for all male and all female patients are 79.6 and 90.0%, respectively, while the corresponding relative 10-year OS rates are 67.1 and 83.5% (Cancerfonden, 2013). Furthermore, a clear trend toward increased survival rates for women with breast cancer has been seen in Sweden (Cancerfonden, 2013) and in the US, while only a small trend toward increased survival was found among men in the US (Anderson et al., 2010). Taken together, these findings suggest that there may be underlying differences in tumor biology between breast cancers arising in men and women, and that these may affect outcome.

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