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Review

Male breast cancer is not congruent with the female disease

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ABSTRACT

It has become customary to extrapolate from the results of treatment trials for female breastcancer and apply them to males with the disease. In the absence of results from national and international randomised trials for male breast cancer (MBC) this appears superficially to be an appropriate response. Closer examination of available data reveals that aspects of the aetiology and treatment of MBC do not fit the simplistic model that men usually have endocrine sensitive tumours which behave like those in postmenopausal women. Most females and males with breast cancer have none of the recognised risk factors, indicating the gaps in our knowledge of the epidemiology of this disease. Several studies have compared epidemiological risk factors for MBC and female breast cancer (FBC) but many have been blighted by small numbers. In comparison with FBC there is a larger proportion of BRCA2 tumours, (occurring in 10% of MBC), and underrepresentation of BRCA1 tumours (found in only 1%), suggesting significant differences in the genetic aetiology of MBC and FBC.

Genome-wide association studies in FBC reported single nucleotide polymorphisms (SNPs) in 12 novel independent loci were consistently associated with disease but for MBC 2 SNPs had a significantly increased risk. Molecular profiles of matched cancers in males and females showed a gender-associated modulation of major processes including energy metabolism, regulation of translation, matrix remodelling and immune recruitment. Immunohistochemistry for kinase inhibitor proteins (KIPs) p27Kip1 and p21Waf1 indicate a significant difference in the immunostaining of tumours from male patients compared with females.

MBC is almost always estrogen receptor positive (ER+ve) and so systemic treatment is usually endocrine. With evidence in FBC that aromatase inhibitors are more effective than tamoxifen in the postmenopausal it was seemingly logical that the same would be true for MBC. Results however suggest less efficacy with AIs and an increase in risk of mortality compared to tamoxifen. The overall survival in male breast cancer was significantly better after adjuvant treatment with tamoxifen compared to an aromatase inhibitor. These important biological differences point the way to the development of new therapies for MBC based on differences rather than similarities with FBC.

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1. Introduction

Because of the relative rarity of male breast cancer (MBC), which comprises <1% of western cases, for men with the disease it has been accepted that trial results derived from its big sister should form the basis for treatment. In the absence of national and international randomised trials for male breast cancer this appears superficially to be an appropriate response. Closer examination of available data suggests that aspects of aetiology and treatment of MBC do not fit the simplistic model that men usually have endocrine sensitive tumours which behave like those in postmenopausal women.

At a microscopic level the major difference between FBC and MBC is the almost total lack of invasive lobular cancers in the latter group since lobular differentiation is an unusual event in males. These very rare cases of invasive lobular cancer may have Klinefelter's syndrome (Sanchez et al., 1986), be taking estrogens as transsexuals (Burcombe et al., 2003) or prostate cancer sufferers (Dore et al., 1982) but predominantly have no known endocrine risk factor (Spencer and Shutter, 2009). One major obstacle to the molecular investigation of MBC is the absence of any human MBC cell line. Such a resource would greatly improve our understanding of this disease.

2. Risk factors

2.1. Endocrine

Most females and males with breast cancer have none of the recognised risk factors, indicating the gaps in our knowledge of the epidemiology of this disease. For a few men, testicular damage, whether from mumps orchitis, high ambient working temperature, use of estrogens or undescended testes increases risk of MBC (Fentiman and Fourquet, 2006). Despite this, in a case-control study of 75 MBC cases, before starting treatment and 75 neighbourhood controls no consistent differences were identified in serum levels of testosterone, prolactin, estrone and estradiol nor in urinary estrogen (estrone, estradiol, estriol), profiles (Casagrande et al., 1988). The only significant factor to emerge was that cases had higher levels of sex hormone binding globulin, associated with greater likelihood of being obese.

Several studies have compared epidemiological risk factors for MBC and female breast cancer (FBC) but many have been blighted by small numbers. Collaboration has been the key to deriving meaningful results. One example is the Male Breast Cancer Pooling Project, which brought together 11 case-control and 10 cohort studies comprising 2405 cases and 52 013 controls (Brinton et al., 2014). The aim was to study potential anthropometric and endocrine risk factors for MBC. Risk was statistically significantly associated with increasing quartiles of weight, height and body mass index (BMI) with the strongest risk predictor being recent rather than historical BMI. It is of interest that gynaecomastia also emerged as being statistically significantly associated with risk, and this was not just a surrogate measure for obesity since it was independent of BMI. This could be interpreted as indicating that in males, an increase in epithelial tissue affects risk whereas women with larger breasts have not been found to be at increased risk of breast cancer (Tavani et al., 1996). The same group used a nested case control design with 101 MBC cases and 217 controls and showed that even after adjustment for ethnic origin, and body mass index there was a significant association between pre-diagnostic serum estradiol and risk of MBC (Brinton et al., 2015). In the highest quartile the odds ratio was 2.47. There was no relationship between androgens and risk.

Preliminary results from 1483 cases amassed by EORTC10085, TBCRC, BIG and the NABCG International Male Breast Cancer Program were reported by Cardoso et al. in 2014 (Cardoso et al., 2014). Of the tumours analysed. 92% were ER +ve (Allred 7/8), 35% PR highly +ve, 87% AR highly +ve and only 5% HER2 +ve. Despite the high level of estrogen receptor positivity, endocrine therapy was given to only 77%. There was a significant improvement in outcome for more recent cases. For non-metastatic cases, median overall was significantly correlated with both ER + ve and PR + ve, less so for ARand unrelated to HER2 status.

Gender differences have been found in the adipocyte regulation of the aromatase enzyme complex (aromatase cytochrome p450 and NADPH-cytochrome p450 oxidoreductase). McTernan et al. (2000) measured P450 aromatase activity in abdominal subcutaneous stromal cells (ASC) and mature adipocytes (AD) from healthy males and females cultured in serum-free medium (McTernan et al., 2000). Whereas ASC aromatase activity increased in females with added cortisol, in males this was inhibited. In mature adipocytes there were no gender-specific differences. Treatment of ASC from pre- and post-menopausal females with either cortisol alone or in combination with insulin indicated significantly different aromatase regulation compared with males.

Using similar methodology, Dieudonné et al. (2006) analysed the activity of type I 11beta-hydroxysteroid dehydrogenase (HSD1) and P450 aromatase in cultured preadipocytes from males and females (Dieudonné et al., 2006). In men, human recombinant leptin upregulated both HSD1 and P450 aromatase) mRNA expression. In women there was down-regulation of both. 17beta-estradiol strongly stimulated HSD1 mRNA expression in women and reduced by 50% P450 aromatase expression. In contrast, 17beta-estradiol did not affect HSD1 expression in men but up-regulated P450 aromatase mRNA.

Studies of steroids in blood and urine may not reflect events at a cellular level so Takagi et al. 2013 measured intratumoural levels of estrogen in MBC (Takagi et al., 2013). Additionally they determined estrogen receptor status in terms of ER α and ERβ together with analysis of estrogen-induced genes, and compared these with results from FBC. There were higher 17β-estradiol concentrations in MBC compared with FBC, although the numbers were small: 4 and 7 tumours respectively. Compared with FBC. MBC tissues more frequently contained aromatase and 17β-hydroxysteroid dehydrogenase type 1 but rarely stained positive for steroid sulfatase. The majority (77%) of MBC were both ERα and ERβ positive, significantly higher than in FBC.

Contrasting results were reported by Dakin Haché et al. (2007) who determined intratumoral aromatase (ITA) expression using tissue microarray (TMA) in a series of 45 cases of MBC treated in the Nova Scotia Cancer Center (Dakin Haché et al., 2007). There was overexpresssion of HER2 in four cases (10%) and 12 (27%) were positive for ITA expression. ITA positive tumours were of less aggressive type fewer being grade 3 or with lymphovascular invasion or nodal involvement and this was manifest in improved survival at 5 years (92% vs. 49%). In contrast, previous work by Santen et al. (1998) had shown immunohistochemical evidence of ITA in 16/26 (62%) of FBC tumours (Santen et al., 1998). There does appear to be a gender difference in relation to this potentially beneficial component of breast cancers.

2.2. Genetics

The Breast Cancer Linkage Consortium collected 164 families with breast/ovarian cancer and germline BRCA2 mutations to evaluate genotype-phenotype correlations (Thompson and Easton, 2001). By the age of 80 years, the cumulative risk of breast cancer in male carriers of a BRCA2 mutation was estimated as 7%. Basham et al. (2002) conducted a study of 94 MBC cases collected in the UK and in contrast no *BRCA1* mutation carriers were identified whereas

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