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Review Article

Risk factors for male breast cancer

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Abstract: Male breast cancer (MBC) presents problems with identification of high-risk groups. Risk factors include hepatic dysfunction, high ambient working temperature, exposure to exhaust fumes and obesity, but none identify a group with a high absolute number of MBC cases. The two significant cohorts are *BRCA2* mutation carriers and individuals with Klinefelter's syndrome (KS), responsible for up to 15% of cases. Since >90% of male tumours are ER+ve, endocrine intervention is logical with the likely agent being tamoxifen. In terms of an acceptable endocrine agent, compliance studies. Compliance studies indicate that men do not tolerate tamoxifen well because of side-effects. Although certain groups with an increased risk of MBC can be identified, the absolute number of cases is small so, at present, a meaningful prevention study is not an option.

Keywords: Male breast cancer, *BRCA2*, Klinefelter's syndrome, tamoxifen, prevention

Introduction

Search for subtle differences which could be exploitable for more gender-specific therapy for MBC is ongoing. One striking difference between female breast cancer (FBC) and male breast cancer (MBC) is the very high rate of tumor estrogen receptor positivity (ER+ve) in males. In a collaborative study of 1483 MBC cases, 99% had cancers that were ER+ve and 82% were progesterone receptor positive [1], implying that endocrine manipulation could be used for prevention. Firstly, a high-risk group has to be identified. Of the numerous risk factors identified the major components are geographical location, obesity, occupation, genetic mutations and Klinefelter's syndrome.

Location

In the developed world, MBC comprises <1% of all breast cancers but, in sub-Saharan Africa a male/female incidence ratio of 1:10 has been recorded [2]. Hepatitis B surface antigen (HBsAg) was present in up to 25% of tested individuals, with the highest rate in Zimbabwe [3]. Resulting hepatic dysfunction increases risk through peripheral conversion of androgens to estradiol. Paradoxically, in Tanzania the incidence of MBC has dropped significantly since the human immunodeficiency virus (HIV) epidemic because of increased mortality [4].

Occupation

Older case-control studies linked MBC to work in hot environments, such as blast furnaces, steel works and rolling mills [5-8]. High ambient temperature overrides the heat exchange mechanism normally maintaining the testes 2-7°C cooler than body core temperature. Heat inhibits spermatogenesis and testosterone synthesis. Steel production in the USA peaked at 111.4 million tons in 1973 and fell to 70 million tons by 1984. In 1974 there were 512,000 steel workers but, by 2020 only 57,800, with many not working close to the heat sources, reducing the potential at-risk group. In the tropics the situation is different. A cross-sectional study from South India assessed thermal stress by wet bulb globe temperature (WBGT) and dehydration from urine color and specific gravity [9]. Of concern, 90% of WBGT measurements were above the recommended threshold limits, associated with excessive sweating, fatigue, and tiredness. Increased mortality from lung cancer, ischaemic heart chronic and liver disease, probably obscures any signal of increased MBC risk.

Table 1. Occupational risk of MBC

Author	Occupation	Study	MBC risk
Mabuchi 1985	Steel making	Case control	7 versus 0
McLaughlin 1988	Printing	Cohort	SIR 3.9
	Perfume making		SIR 7.6
Lenfant-Pejovic 1990	High temperature	Case control	OR 2.8
Cocco 1998	High temperature	Case control	OR 3.4
Hansen 2000	Gasoline & exhaust	Case control	OR 2.5
Ma 2005	Firefighters	Cohort	SMR 7.4
Kendzia 2022	Welders	Case control	OR 2.07

SIR, standardized incidence rate. OR, odds ratio. SMR, standardized mortality rate.

Table 2. Risk of MBC with BMI and age (Swerdlow 2021)

Variable	OR	95% CI
BMI age 20 per 2 unit change	1.07	1.02-1.12
BMI age 40 per 2 unit change	1.11	1.07-1.16
BMI age 60 per 2 unit change	1.14	1.09-1.10

A Danish study of occupational exposure to petrol and exhaust fumes included 12,880 controls and 230 MBC cases, with a 2.5-fold increase in odds ratio (OR) for MBC with an estimated lag time of >10 years [10]. The OR rose to 5.4 among men aged <40 when first employed. Florida firefighters have reduced overall mortality from cancers but more deaths from MBC [11]. Carcinogens in exhaust emissions include polycyclic aromatic hydrocarbons, benzene, toluene and 1.3-butadiene, present in both tumors and benign tissue [12]. Wide variation in DNA (deoxyribonucleic acid) adduct levels may partly result from DNA repair gene polymorphism [13].

Welding fumes are carcinogenic, containing iron, nickel, molybdenum and indium tin oxide [14]. In a European multi-center study with 644 cases and 1,959 controls, welding histories were linked up with a measurement-based exposure matrix [15]. Lifetime exposure to welding fumes above the median of exposed controls was associated with a doubling of the risk of MBC (OR 2.07). Results are summarised in **Table 1** and despite revealing risk factors do not delineate a high-risk group.

Obesity

Obesity is the most common cause of hyperestrogenisation in males and is associated with at least a doubling of MBC risk [16-19]. Similarly, there is a doubling of risk for diabetics as vascular disease leads to testicular dysfunction in up to 90% [18, 20, 21]. Swerdlow et al conducted an interview population-based study with 1998 cases and 1597 controls [22]. MBC risk increased significantly with increasing body mass index (BMI) and age, as shown in **Table 2.** There was an even stronger association between large waist circumference five years before interview. Although significant, because it is common, obesity does not define a manageable high-risk group for a prevention study.

Genetics

Between 5 and 10% of MBC cases are due to autosomal dominant inheritance, mostly *BRCA2* mutations [23]. The risk of MBC in *BRCA2* mutation carriers is 8.9% to age 80 [24]. Using exome sequencing in a cohort of 50,726 volunteers, there were pathogenic mutations in 267 (0.5%), 95 *BRCA1* and 172 *BRCA2* [25]. Compared with clinical ascertainment, exome sequencing-based screening increased the identification of mutation carriers fivefold.

The role of the androgen receptor (AR) in the etiology of MBC is contentious. Within exon 1 of the AR gene, a polymorphic region containing a variable number of and shorter cytosine, adenine, and guanine (CAG) repeats increases transactivation of the receptor [26]. In 53 MBC cases and controls, Young et al found no overall difference in the length of CAG repeats and no controls had >28 repeats whereas, 2 MBC cases had 29 and 30 repeats [27]. In contrast, a Finnish study screening the entire AR coding region and CAG repeats in 32 cases found no germline mutations and no difference in CAG repeat lengths, concluding that AR gene mutations did not significantly affect risk [28]. Analysis of tissue microarrays from 1984 MBC cases showed that FOXA1+ve and AR+ve tumors were associated with better disease-free survival in ER+ve cases [29]. The authors suggested that AR blockade was a feasible therapeutic approach.

Klinefelter's syndrome

Of newborn boys, 0.16% have Klinefelter's syndrome (KS), with at least one X chromosome added to the normal XY karyotype (most frequently 47XXY). Swerdlow et al followed a cohort of 3518 individuals with KS for an average of 15 years: 3002 (85%) were 47XXY and 320 (9%) 47XXY/XY mosaic [30]. They reported that the standardized incidence ratio (SIR) for MBC was significantly elevated at 19.2 and the standardized mortality rate (SMR) greatly increased at 57.8. Comparing those having a 47XXY karyotype with men having a 47XXY/46XY mosaic, the latter group had a higher SMR for MBC (223 versus 29). Reviewing these findings, although there was a 20-30-fold increase in risk compared with the male population, Brinton pointed out that this was lower than that of the UK female population (SIR = 166) [31].

Using DNA from 1355 MBC, Moelans et al performed massively parallel sequencing, targeting all exons of 1943 cancer-related genes and reported that 5 (4%) cases had KS and 5/44 (11%) with paired normal tissue had pathogenic *BRCA2* germline mutations [32]. By joining these disparate risk factors, possibly up to 15% of men who will develop breast cancer could be identified and offered surveillance in the context of a randomized controlled trial (RCT).

The larger studies of KS have not given the age at diagnosis of MBC, but the case reports and small series show a median age of 57 (range 50-69) [33-36]. On this basis, the appropriate age group for surveillance would be aged 50-70. In the UK, there are approximately 55,000 individuals with KS, in the US, 269,000 have KS. These are enough to generate an adequately powered RCT.

Gynecomastia

Self-limiting gynecomastia is common in pubertal boys and, there is an increased incidence in later life, often spontaneously regressing [37]. Histologically, the incidence of gynecomastia in mastectomy specimens from MBC cases was 21%, less than the 40-55% in unselected autopsy cases [38]. Several older studies found no linkage between gynecomastia and MBC [39-41].

Evidence of a possible association of gynaecomastia with MBC risk came from an investigation of discharge records from the US Veterans Affairs Medical Care System [42]. Among the 4,501,578 men, there were 642 cases of MBC. Conditions significantly related to risk included diabetes, obesity, orchitis, Klinefelter syndrome and gynecomastia. After adjustment for obesity, the diabetic risk disappeared, but gynecomastia remained a significant risk factor. The diagnosis of gynaecomastia was not defined, comprising both true and pseudo gynaecomastia. In some cases, the breast lump may have been a missed MBC.

Coopey et al reviewed histopathology specimens from 932 males undergoing excision biopsy or mastectomy looking for atypical ductal hyperplasia (ADH) [43]. ADH was present in 19 cases of gynecomastia, 13 being bilateral. After a mean follow-up of 75 months, no breast cancers occurred, suggesting ADH in males carries a lower risk than for females. Most studies indicate that gynecomastia is not a significant risk factor and does not identify a manageable high-risk group.

Endocrine risk factors

Case-control studies examining serum and urinary hormones in MBC showing results that have mostly yielded negative results [44-47] except one which reported increased levels of estradiol in cases [48]. Testicular damage from mumps orchitis aged >20, undescended testes, congenital inguinal hernia and orchidectomy can result in low testosterone levels, an uncommon risk factor for MBC [49].

Diet

Hsing et al interviewed the next of kin of 178 men who had died of MBC and 512 men who had died of other diseases to obtain data on diet, exercise, height, weight, occupation, use of alcohol and tobacco [17]. They found a non-significant trend of increased risk with consumption of red meat and a decrease with higher intake of fruit and vegetables. Higher socio-economic status was associated with increased risk (OR = 1.8, CI 1.1-3.0).

Using data from 10 cancer registries, Rosenblatt et al conducted a study of diet in 220 cases of MBC and 291 controls derived by ran-

dom digit dialing [50]. There was no association between intake of fat, carbohydrate, or protein fiber. Contradictory results are unsurprising since, until recently, the same situation existed for diet and risk of FBC. It took a cohort study of 188,736 postmenopausal women, of whom 3501 developed breast cancer, to show that a doubling of the percentage energy derived from fat significantly increased risk (HR 1.15) [51]. In the UK Women's Cohort Study of 35,372 women, 283 developed premenopausal and 395 postmenopausal breast cancer [52]. In postmenopausal women, the hazard ratio was 1.1 for each 50 g of meat per day. These significant but small effects would be undetectable in the male case-control studies so far conducted.

Alcohol

Evidence accumulates that alcohol consumption is a risk factor. Earlier studies of cirrhotic males had shown no increased risk, possibly confounded by the high mortality from cirrhosis and the rarity of MBC [17, 20]. Nevertheless, a large Danish study of 11,642 cirrhotic men, with relatively short follow-up (4.3 years), found a fourfold increase in the expected number of cases of MBC [53].

A European multi-centre study with 74 cases and 1432 population controls reported a significant relationship between alcohol consumption and MBC risk [54]. The odds ratio for alcohol intake >90 g/day was 5.89 (CI 2.21-15.69). The risk rose by 16% per 10 g of daily alcohol intake. A bigger study of 1457 MBC cases and 3374 population controls found a similar effect [55]. The high mortality rate in cirrhotics precludes any MBC study.

Ionizing radiation

Exposure of the breasts to ionizing irradiation increases FBC risk and there is some evidence of a similar effect in males [56]. In a study of 75 MBC cases, using neighbourhood controls matched for age and ethnicity, there were no significant differences in exposure to fluoroscopy, repeated chest X-rays, or upper body irradiation, but excess risk associated with ≥10 fluoroscopies [47]. Thomas et al reported a modest increase in risk with repeated chest X-rays or upper body irradiation in a case-control study of 227 MBC cases [57]. The effect emerged 20-35 years after exposure and declined after 40 years.

Using data from the Hiroshima and Nagasaki Tumor Registries, Ron et al reported 9 cases of MBC among 45,880 male atomic bomb survivors [58]. There was a dose response relationship with a significant 8-fold increase in risk per sievert. These conflicting data may result from a long latent period from exposure, so differences in length of follow-up may miss a significant effect of radiation.

Wang et al examined the incidence of MBC after childhood cancer in a systematic review of 38 publications and analyzed data in the PanCareSurFup cohort [59]. The cohort-specific frequencies of MBC were between 0 and 0.40% after follow-up from 24 to 42 years. In the cohort of 37,738 males, there were 16 cases of MBC (0.04%), representing a 22.3-fold increased risk compared with the general male population. Male survivors of childhood cancers have an elevated propensity for MBC, but absolute numbers are low.

Problems with prevention

To conduct a prevention trial with any hope of success, a high-risk group has to be identified. Additionally, an effective, non-toxic, relatively inexpensive intervention is required. There are outstanding problems with each of these criteria. The individuals at high risk of MBC will be a heterogeneous group, including those carrying *BRCA2* mutations. Genetics based clinics could provide these individuals, as could others with Klinefelter's, although some of them would have been diagnosed in male infertility clinics.

Potential agents

For women involved in prevention trials, the main agents tested were the selective estrogen receptor modulator (SERM) tamoxifen [60], aromatase inhibitor anastrozole [61] and the steroidal aromatase inhibitor exemestane [62]. It is logical to test one of these agents in men at risk of MBC since the cancers are almost invariably ER+ve. In the IBIS-II trial, there were 48 ER+ve cancers diagnosed in the anastrozole arm versus 103 in the control arm (HR 0.46).

There are however, problems with gender differences in compliance and efficacy. Men are

less likely than women to accept side effects. Three cancer centres have reported side effects in MBC cases receiving adjuvant tamoxifen [63-65]. These included reduced libido, weight gain, hot flashes and mood alterations. As a direct result, >20% stopped tamoxifen within a year of diagnosis, compared with only 10% of females. With these levels of non-compliance in men diagnosed with breast cancer how much more difficult will it be to persuade males at risk to take tamoxifen?

Aromatase inhibitors (AIs) are ineffective in MBC. In a SEER-derived analysis of 124 MBC cases, 95 received tamoxifen and 19 an aromatase inhibitor [66]. Cancer mortality was lower in those receiving tamoxifen compared with no adjuvant therapy but there was no benefit from adjuvant AIs. In a series of 257 German MBC patients with ER+ve cancers, 207 received tamoxifen and 50 were prescribed AIs [67]. After 42.2 months, there were 47 (18%) deaths in the tamoxifen group compared with 16 (32%) in the AI group, a 1.5-fold increase. In a study of 316 FBC and 158 MBC treated with adjuvant tamoxifen, together with 60 FBC and 30 MBC given AIs, the 5-year overall survival of FBC and MBC patients given tamoxifen was similar: 85% versus 89% [68]. In contrast, FBC patients given AIs had significantly better survival than MBC cases 85.0% versus 73.3% ($P = 0.028$). The gender difference in efficacy of adjuvant AIs may relate to testicular estrogen synthesis, unaffected by AIs [69]. Approximately 20% of male estrogen originates from the testes. This means that if men are given an AI, it should be combined with a gonadotropin releasing hormone (GnRH) analog (GnRHa) to stop testicular stimulation by the hypothalamus but with an increase in side-effects such as hot flashes.

Reinisch et al measured changes in serum estradiol levels in 56 MBC cases after three months of therapy with tamoxifen alone, tamoxifen plus GnRH analog (GnRHa) or an aromatase inhibitor plus GnRHa [70]. Median estradiol levels increased by 67% with tamoxifen, decreased by 85% with tamoxifen plus GnRHa, and decreased by 72% with AI plus GnRHa. Both sexual function and quality of life were worse with added GnRHa. This illustrates the limited repertoire of endocrine candidates for MBC prevention.

In the absence of prevention, it is necessary to revert to early detection and indeed, the screening programmes have successfully picked up small cancers in women. For males, mammography can be painful and time-consuming. In contrast, although requiring an expert ultrasonographer, ultrasound scans would be a reasonable approach for men at risk. Early detection could be examined in a multicenter randomized controlled trial (RCT) comparing annual ultrasound with annual clinical examination. The target group would comprise men with KS and carriers of *BRCA2* and occasionally *BRCA2* mutations. Unfortunately, although there is a significantly elevated standardized incidence ratio (SIR) of 21.3 this is derived from a population of 3518 KS cases, followed for 15 years in which there were 4 cases of MBC [30]. Hence, the logistics of conducting a trial for this group appear daunting because of the rarity of MBC.

Conclusions

At present, there are no outstanding candidate agents for the prevention of MBC, but there is scope for an RCT of early detection in those at increased risk with Klinefelter's syndrome or being carriers of *BRCA2* mutations. A possible trial could compare annual clinical examination versus annual clinical examination plus bilateral breast ultrasound. Such a study would need national and international support and provide an opportunity for broader recognition of this rare but potentially fatal disease.

Disclosure of conflict of interest

None.

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