Male Breast Cancer: a review of risk factors

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Abstract
Male breast cancer (MBC) is so rare and uncommon that every year in USA and UK, only 0.5-1% of the patients diagnosed with breast cancer are men and among all men's cancer-related deaths less than 0.1% are caused by MBC. In this review article the most important and well-known risk factors of MBC including age, race, genetics and family history, ratio of estrogen to androgen, hormone receptors, Klinefelter's Syndrome, Cowden's Syndrome, life style, and environmental exposures are discussed.

Keywords: Male breast cancer, Breast cancer, Risk factor

Epidemiology
Male breast cancer (MBC) is so rare and uncommon that every year in USA and UK, only 0.5-1% of the patients diagnosed with breast cancer are men and among all men's cancer-related deaths less than 0.1% are caused by MBC (1-5). However, it is reported that male-to-female breast cancer ratio in African developing countries is more than developed ones (6, 7). These higher rates can be explained by hypoestrogenism caused by endemic hepatic infectious diseases (8, 9). In SEER Cancer Statistics Review that includes statistics from 1975 through 2006 it is reported that the incidence of MBC has
risen since three decades ago (10). Compared to female breast cancer (FBC), MBC occurs not only at ages older than FBC (60 versus 53 years), but also with more metastatic or advanced stages and higher probabilities of HR positivity (11-14).

Risk factors

Age

As indicated in previous literature the incidence of MBC rises with age (3, 10). However, the age of diagnosis for males and females are slightly different. Men are usually diagnosed around the age of 68 while women's average diagnosis age is 61 (10, 15), but this difference between males and females regarding the incidence age of breast cancer is not reported to exist in Asia and Middle East (16-19). Based on a study investigating 1396 MBC cases from 1985 to 2000 in Florida, the age-adjusted incidence rate since 1990, which was 0.9 cases per 100,000, increased significantly to 1.5 cases per 100,000 in 2000 (20).

Race

It has been reported that MBC is more common among black men in comparison with other races. For example, in central Africa and Tanzania 6% of the men's cancers are MBCs which is nearly 6 to 12 times higher than countries with the majority of white men (7). In USA, the number of MBC among black men is higher than white men (21). Moreover, it has been found that black men have inferior chance for survival regarding MBC compared to white men who have been reported to have higher 5-year overall survival (22). In a recent study, Sun and colleagues reported several differences between black men and other races concerning the MBC. It was shown that not only black men were more likely to be in stages II to IV but also their tumours were more advanced compared to men of other races. Moreover, black men who were diagnosed with MBC
showed higher lymph node involvement and lower ER and PR positive rates. Another important point is that in cases of black men, the rates of distant metastasis were higher than other races. Finally, they found that black men had significantly poorer rates of overall survival compared to other races (23).

**Genetics and family history**

One of the major risk factors regarding MBC is family history. It has been reported consistently in several studies to have contributions in MBC (12, 24-28). Multiple studies reported significant relationship between survival rate and having a BRCA mutation especially BRCA2 (29-34). Also, it has been found that male carriers of BRCA2 get MBC about 10 years earlier and have more aggressive and advanced disease (35, 36). When this gene, which is on chromosome 13q22, is mutated, it causes tumourigenesis and problems for genomic integrity (37). Most of the previous works which studied the role of BRCA mutations in increasing the risk of MBC have reported that unlike BRCA2, BRCA1 was very uncommon and less than 5% of the men were carrying this mutation (34, 35, 38, 39). Among all the men who possess BRCA2 mutations, five to 10 percent get breast cancer (40, 41). In a study conducted by Ottini and colleagues, luminal B and HER2 positive subtypes were reported to have associations with high tumour grade and BRCA2 (42). Deb and colleagues reported that BRCA1/2 and BRCA X is MBC cases are different from the FBC ones. In FBC cases, a clear BRCA1 phenotype can be seen, but in MBC cases this clear BRCA1 phenotype is not evident and instead of that there is a possibility of a BRCA2 phenotype of micropapillary histological subtype (43). Although mutations in BRCA2 has been reported to have the most involvement in MBC, mutations in other genes such as PTEN tumour suppressor gene, TP53, and PALB2 are also reported to be responsible for MBC (44-49). There are other kinds of mutations which are
responsible for breast cancer in females such as BRIP1 and RAD51C. However, these mutations have not been reported to have any effects regarding the increase risk of MBC (50, 51). It has been reported that mutation in CHEK2 is associated with increased risks of FBC (52). Not only does mutation in CHEK2 1100delC contribute to 9% of all MBC, but it also increases the risk of MBC ten times in men who do not have BRCA mutations (53, 54). Moving from north Europe to south, a decrease in the CHEK2 1100delC mutation frequency can be seen, which suggests that CHEK2 1100delC mutation is varied by geography and different ethnic groups (55-59).

**Alteration of the ratio of estrogen to androgen**

Higher proportion of estrogen to androgen increases the risk of MBC development. Moreover, other problems such as obesity, abnormalities in testicles, hormonal therapies, hepatic dysfunction, thyroid disease, marijuana use, or liver disease may lead to higher estrogen to androgen levels and thus are linked to MBC (25, 27, 28, 60, 61). Obesity has found to be a risk factor for MBC, but more research is required to consider it as an established risk factor (27, 62-65). Testicular dysfunction has reported to be linked to MBC in several studies (8, 12, 66). Some of the most common abnormalities in testicles which have been found to have links to higher risks of MBC incidence are orchitis, orchiectomy, undescended testes, and congenital inguinal hernia (7, 67-71). Production of androgen is decreased because of these abnormalities. Therefore, the ratio of estrogen to androgen will increases and thus leads to higher risks of MBC.

**Hormone receptor**

Several studies have shown that the status of hormone receptor and nodal involvement are factors with the most prognostic role on MBC (72-81). In a study it was shown that immunonegativity of estrogen receptor (ER) and progesterone receptor (PgR) had a
significant negative relationship with breast cancer prognosis (80). Since androgen receptor (AR) affects the inhibition of signals dependent on estrogen, it can be regarded as a potential marker in breast cancer prognosis (5, 82-85). Moreover, it has been found that AR positivity, which was detected in 70-80% of all cases of breast cancer, can change the outcomes of the disease in favor of the patients especially those who had ER-positive tumours (5, 83, 86-88). Also, AR positivity has a significant relationship with the expression of other steroid related receptors such as progesterone and estrogen (72). Therefore, it seems that AR positivity is a favorable factor which reduces the MBC risk and increases prognostic factor for the disease and its survival chance (72).

**Klinefelter's Syndrome**

Klinefelter's syndrome is caused when a male is born with more than one X chromosome (69, 89-91). Many studies showed that this syndrome has a positive relationship with higher incidence of MBC in a way that nearly 7% of men who were diagnosed with MBC had also Klinefelter's syndrome (67, 89-92). Klinefelter's syndrome leads to higher levels of gonadotropins and follicle-stimulating hormone. When these higher levels are accompanied by lower levels of androsterone, the ratio of estrogen to androgen will increase (71, 93, 94). This higher ratio may lead to invasive breast cancer by proliferating the cells of ductal breast cancer (71, 93, 94). Moreover, it was reported that men who had Klinefelter's syndrome are not only diagnosed earlier with MBC than others but also have 14-50 times higher risk of developing breast cancer (94).

**Cowden's Syndrome**

Cowden's syndrome's most know characterization is multiple hamartomas (95-98). As stated before mutations in some genes may lead to MBC. One of them is PTEN which is a tumour suppressor gene. In 13-81% of families with Cowden's syndrome, PTEN
mutations are found and based on ascertainment criteria, PTEN locus is linked to loss of heterozygosity in a subgroup of Cowden's syndrome tumours (99-105). In several studies, Cowden's syndrome has been reported to be a risk factor for MBC and the reason is probably lies in its link to PTEN mutations (44, 105, 106).

Life style and environmental exposures
Although a small study showed that using alcohol excessively is related to MBC(107), lifestyle risk factors such as smoking, ionizing radiation, polycyclic aromatic hydrocarbons, red meat, electromagnetic radiation, or consuming alcohol have not been consistently reported to have any associations with higher risks of MBC (108). There was a case of marines who were exposed to solvents through drinking water from 1950-1985. These marines were diagnosed with MBC, but this relationship was not proved to be a cause-and-effect one (109). Moreover, several other case studies have tried to find association between breast cancer and electromagnetic radiations, but most of the results were insignificant (25, 110-116). Lack of exercise was reported to have a negative relationship with MBC and obesity was reported to have a positive relationship (27). The surprising finding of Brinton et al. was the positive association between MBC and history of bone fractures (27). Although Rosenbaum and colleagues found no relationship between MBC and exposures to electromagnetic fields, they reported positive association between MBC and heat exposure (117).

Conclusion
Based on the presented studies it can be concluded that breast cancer is more common in women than men and it tends to present itself in older men. Also, the ratio of male-to-female breast cancer in African developing countries is higher. Not only are black men at more risk of MBC, but also their tumours have been reported to be at more advanced
levels compared to other races. Genetics plays a major role in MBC in a way that 5 to 10 percent of men who possess BRCA2 mutation get MBC. Another factor is the ratio of estrogen to androgen. Higher proportion of estrogen to androgen increases the risk of MBC development. The status of hormone receptor and nodal involvement are factors with the most prognostic role on MBC. Syndromes such as Klinefelter and Cowden have been reported to have positive correlation with MBC. Most studies have not found statistically significant relationship between lifestyle and environmental risk factors such as smoking, ionizing radiation, polycyclic aromatic hydrocarbons, red meat, electromagnetic radiation, or consuming alcohol and MBC. However, in one study, it was found that lack of exercise has significant positive relationship with MBC. More studies on different risk factors and the significance of their effect is suggested.

References

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