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Oncology | Review article

Male Breast Cancer: Another Look

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Abstract

Everybody is born with the mammary gland. Mammary gland development occurs through various stages throughout embryonic, and stays dormant for males. Although it is uncommon, male also gets breast cancer, occasionally. Male breast cancer accounts for approximately 1% of all breast cancer cases, and it is increasing. When compared with other rare diseases, male breast cancer is understudied. Typically, male breast cancer is treated in the same way as female breast cancer. In this article, the various aspects and attributes of male breast cancer and its treatment methods are reviewed.

1. Introduction

Everybody, female or male, is born with that mammary gland (breast). The mammary gland is a complex secretory organ, with a number of cells, including epithelial cells, adipocytes, vascular endothelial cells, and other [1]. The mammary gland development occurs through various stages throughout embryonic, puberty, and reproductive life. Before the onset of puberty, the development of male and female breasts are alike. Puberty initiates the release of hormonal signals, such as estrogen and progesterone which induce the maturation of female breast tissue, specifically the ductal and connective tissue [2]. Diversely, males excrete androgen hormones which limit stromal and ductal growth, leading to the atrophy of ducts and a large fat content by volume [3]. Additionally, the adult male breast lacks Cooper ligaments and terminal duct lobular units are sparse compared to female breast tissue [4]. Hence, though it is uncommon, male also gets breast cancer, occasionally. Men are more likely to ignore a lump in their breast, and hence are much less likely to detect breast cancer in early stages and tend to present at higher stages than women, at diagnosis.

Worldwide cases of male breast cancer (MBC) uncommon hitherto is on the rise off-late [5], triggering renewed interest in exploring the causes, risk factors, symptoms, diagnosis and treatment for the disease. Large data is not available due to limited research in the area and the available data base is due to retrospective study over the decades. Treatments have been recommended based on the extrapolation from study trials on women cancer patients [5].

Study by the Dutch between 1972-2016 reports that transgender women on feminine hormone therapy have a higher risk of breast cancer when compared to a normal male while it is lower compared to normal women. In case of transgender men on masculine hormone therapy the risk of breast cancer is lower compared to average women [6].

2. Epidemiology of male breast cancer

The American Cancer Society estimated that about 268,600 new cases of female breast cancer will be diagnosed and about 41,760 women will die in the United States for 2019. It is expected that 2,670 new cases of invasive male breast cancer will be diagnosed and about 500 men will die in the United States for 2019 as shown in Figure 1 [7]. These figures show a 20% higher mortality rate is for male breast cancer compared to females.

About 0.98% of breast cancer will be diagnosed in men and 1.04% of breast cancer death will occur in men. This indicated a climb in incidence of the male breast cancer. In 2016, the lifetime risk of a male being diagnosed with breast cancer is about 1 in 1,000 [8]. In 2019, the lifetime risk of a male getting breast cancer is about 1 in 833 [7]. Because the incidence of male breast cancer is rising, there has been an increasing interest in this disease.

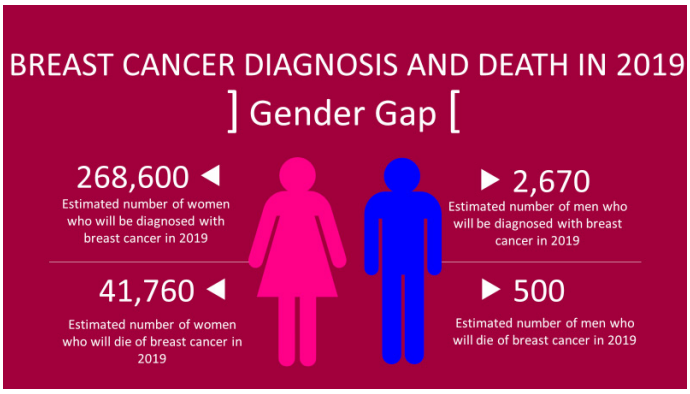

Figure 1. Estimated breast cancer cases and death in 2019. Figure drawn based on the estimation of American Cancer Society [7].

3. Ethnicity

A meta-analysis on 1,201 male and 36,172 female breast cancer patients from 27 African countries was done in Africa on male breast cancer based on limited database from several years for reliable characterization [9]. A male to female ratio of >6% was reported in an African geographic band but the overall ratio of 0.042 has seen a considerable decrease; 0.027 (95% CI: 0.017e0.045) in North African countries and 0.049 (95% CI: 0.039e0.061) in Sub-Saharan countries. In the USA, studies reveal that African American women have a relatively lower incidence of breast cancer compared to white females while the African American males have a higher incidence compared to their white counterparts [9].

The disease being rare among men etiology and mode of treatment is mostly based on the studies on female patients. Studies have indicated that the diagnosis age (weighted average) in African men was 54.6 years and 47.7 years in women with increase in gap over recent years. In the United States the corresponding age was 67 and 61 for men and women respectively. Increase in life expectancy of African men might have contributed to the late diagnosis along with lack of awareness [9] and breast enlargements in young men misdiagnosed as gynecomastia while studies have shown that it was present in 6-38% of breast cancer cases in men [10]. Incidence of cancer being high in premenopausal women as they undergo rapid changes in reproductive factors and life style.

The most common type of breast cancer reported in men across most of the population is the infiltrating ductal carcinoma [10] with an incidence of 65 to 95% with peak incidence at 71 years. As reported in US Surveillance, Epidemiology and End Results (SEER) registry, male breast cancer was more hormone receptor positive (progesterone receptor 75% and estrogen receptor being 82%), while African women tend to have a negative hormone receptor and triple-negative breast cancer. It is reported by studies that nearly 10% of the African men with the disease have genetic influence of breast and ovarian cancer.

SEER cancer statistics review 1975-2016 indicates that incidence rate of breast cancer is more in black males than white males. But it is opposite in case of females (incidence rate is high in white females than black females) [11]. Figure 2 gives the incidence rates of breast cancer in both sexes over the years 2010-2016. Black females with breast cancer have poorer survival than do white females, but little is known about racial disparities in male breast cancer [12]. Figure 3 shows the mortality rates of breast cancer in both sexes over the years 2010-2016.

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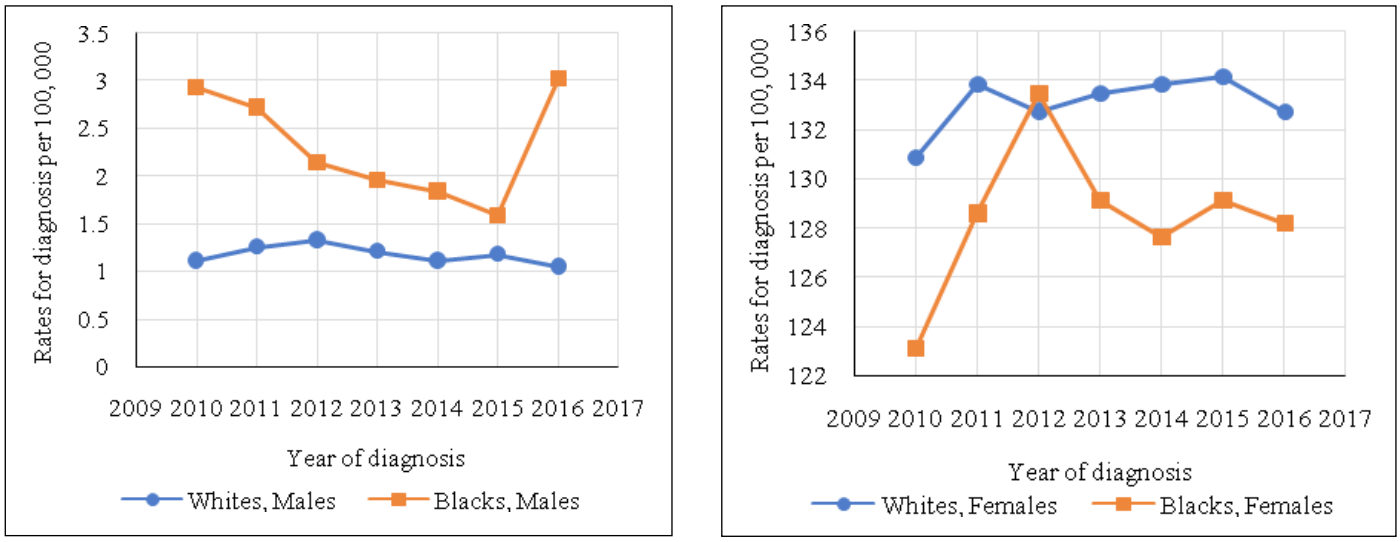

Figure 2. Incidence rates of breast cancer in both sexes over the years 2010-2016. Graph drawn based on SEER's cancer statistics review 1975-2016 database [11].

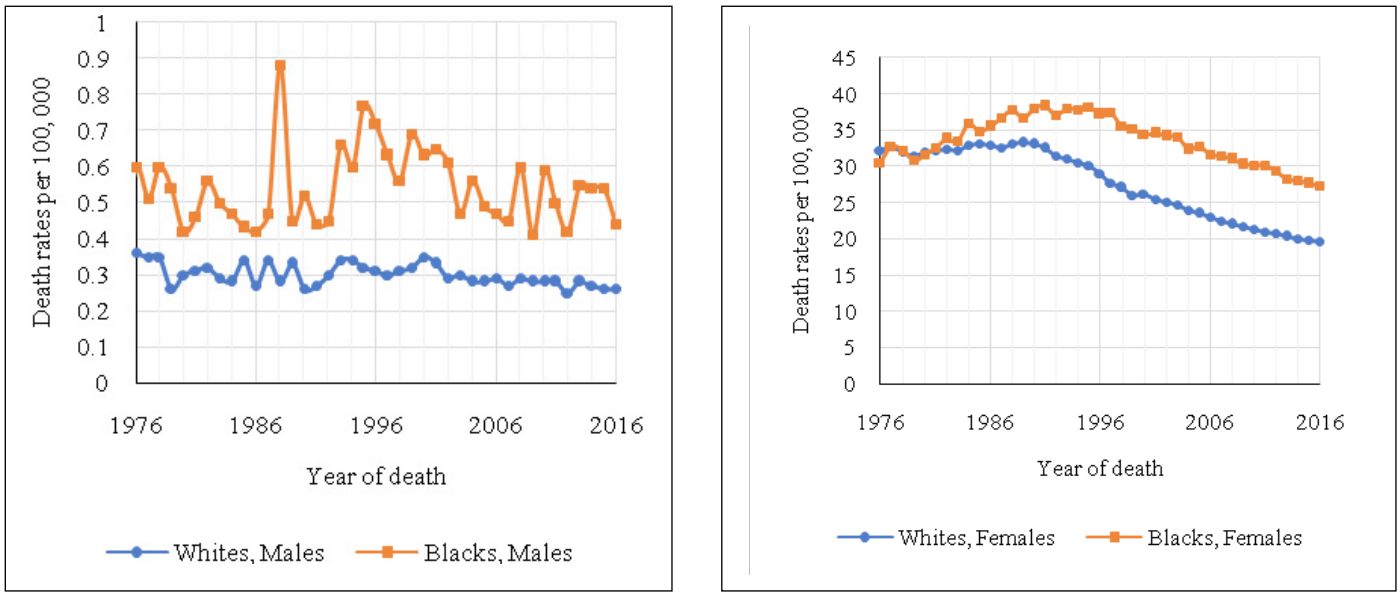

Figure 3. Mortality rates of breast cancer in both sexes over the years 2010-2016. Graph drawn based on SEER's cancer statistics review 1975-2016 database [11].

4. Genetic factors and Biomarkers

Male breast cancer anatomy, morphology, and occurrence can be influenced by a variety of factors such as chromosomal abnormalities. Klinefelter syndrome, an individual possessing XXY chromosomes, increases the risk of being diagnosed with breast cancer by 50 times [4]. Male breast cancer also possesses a hereditary component. Approximately 20% of male breast cancer patients have a first degree female relative who's also been diagnosed with breast cancer [13]. Genetic mutations with a high penetrance such as BRCA 1 and BRCA 2 are also a risk factor. BRCA 2 mutations are commonly found in men with breast cancer, occurring within 4%-16% of cases while the BRCA 1 mutation is less common, making approximately 0%-4% of cases [4]. The majority of male breast cancer tumors are hormone receptor positive, 90% of diagnoses [13].

5. Subtypes and Characteristics

ACancer that begins in the milk ducts is called ductal carcinoma. Invasive (infiltrating) ductal carcinoma (IDC) is the most common occurring type of breast cancer in men. IDC occurs when cancer cells spread beyond the lining of breast ducts [14]. The histological features of male IDC are similar to female IDC, malignant glands causing stromal desmoplasia [4]. Ductal carcinoma in situ constitutes about half of the cases and is found in the lining of the duct [4,14]. Papillary carcinoma makes up 2.6% of male

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breast cancer diagnosis and is 2x more likely to occur in men [4]. Papillary carcinomas are typically non-invasive, intracystic, and consist of 2 cell layers. The ductal epithelial cell layer and myo cell layer have a vascular core which are lacking in malignant papillary lesions. Rates of proliferation amongst the ductal epithelium vary.

Cancer that begins in the milk-producing glands is known as lobular carcinoma. This type is rare in men because men have few lobules in their breast tissue [15]. Invasive lobular carcinoma occurs in 1.5% of cases and is associated with Klinefelter's syndrome [4]. Invasive lobular carcinoma lacks tubular formation and is typically discohesive and dispersed through fibrous stroma. In situ lobular carcinoma hasn't been found in men [14]. Primary or secondary breast lymphoma are typically related to non-Hodgkin-B-cell lymphoma [4]. Histological features vary, but tumors typically have a high nuclear-to-cytoplasm ratio and are disjointed. Inflammatory breast cancer is characterised as a type of cancer where the breast is warm, swollen, and red [14]. Paget disease of the nipple is an additional male breast cancer that is characterised as a tumor growing to the surface and originating from the ducts (PDQ, 2021). Malignant lesions are rare but typically travel from more commonly occurring cancers such as prostate or lung [13].

Most of the male breast cancers are estrogen receptor positive (ER+). In a study, out of 1,483 patients, 92% of male patients had ER+, 5% had human epidermal growth factor receptor 2 positive (HER2+), and 1% had triple negative breast cancer (TNBC) [16]. ER+ female breast cancer frequency varies with menopausal status, but the proportion typically lies between 64% and 79% [17]. Around 20% of female breast cancer are HER2+ and 10-15% are TNBC [18]. Some men inherit abnormal (mutated) genes from their parents that increase the risk of breast cancer. In normal cells, BRCA1 and BRCA2 genes help make proteins that repair damaged DNA [19]. DNA damage can be caused by mutations, carcinogen exposure, Loss of heterozygosity, stress or ionizing radiations. When a tumour suppressor gene is mutated, cell growth may be promoted. Impaired DNA repair may elevate the risk of malignant transformation of breast cells due to the accumulation of spontaneous mutations in target genes (Figure 5) and increasing susceptibility to exogenous carcinogens [20]. Mutations in one of several genes, especially a gene called BRCA2, may put him at greater risk of developing breast and prostate cancers [21]. If a man has a strong family history of cancer, he may carry genes that increase the risk of breast cancer.

As per the reports from SEER with study on 2000 cases, state that 93.7% were ductal/unclassified carcinomas, 2.6% papillary, 1.8% mucinous, and 1.5% lobular in contrast to 12% lobular in women. High rate of hormone-receptor expression is seen in male breast cancer with 90% expressing estrogen receptor and 81% expressing progesterone receptor unlike in females and in both cases the rate increases with age [5,22]. On the contrary, as per the study on 75 patients the proto-oncogene, her2-neu are not expressed significantly (only 5%) in male breast cancer [5,23].

Difference between male and female breast is shown in Figure 4 [24]. Breast is composed of two types of tissues, namely glandular and stromal tissues. Glandular tissues consist of the milk-producing glands (lobules) and the ducts (the milk passages). Stromal tissues include fatty and fibrous connective tissues of the breast [10,11,12,25,26]. Breasts with more fibrous tissue than fatty tissue are considered dense. Female breast tissue consists of milk-producing glands (lobules), ducts that carry milk to the nipples, and fat. Male breast consists of ductal structures within collagenized stroma, with no/rare lobular elements [27]. During puberty, female begin developing more breast tissue, and male do not. Men are born with a small amount of breast tissue, so they can also develop breast cancer. Figure 5 shows a summary of the various causes of male breast cancer, as reported by George and Shuka [20].

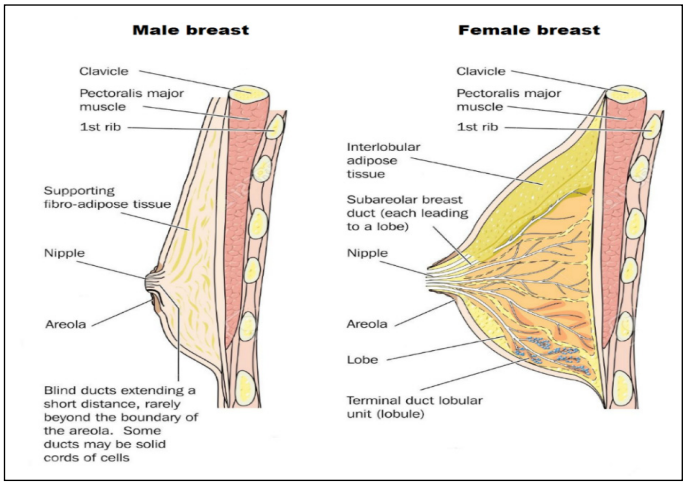

Figure 4. Difference between male and female breast [24].

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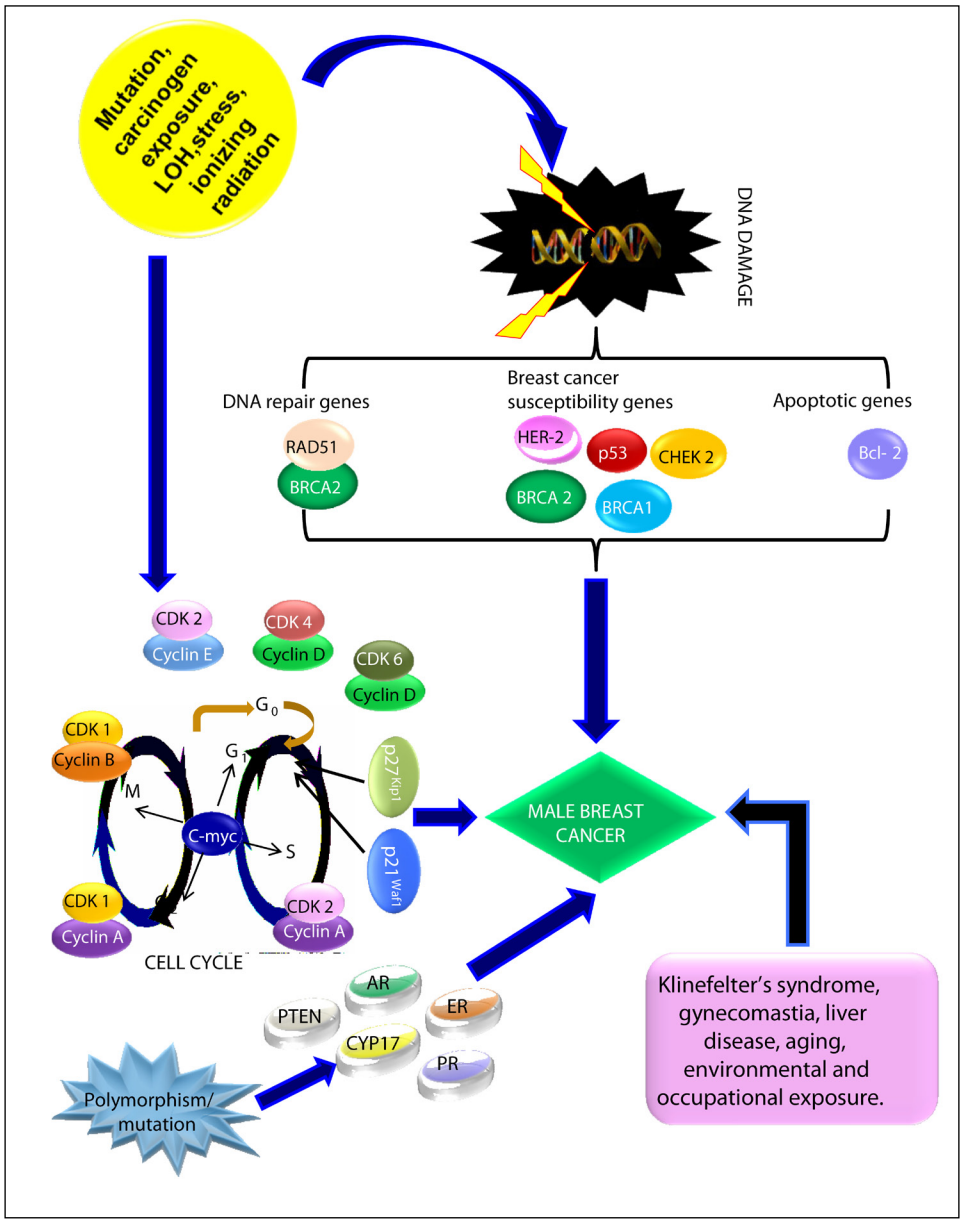

Figure 5. Possible causative factors for male breast cancer [20].

6. Signs and symptoms of male breast cancer

The signs and symptoms are similar to female breast cancer, which include a painless lump or thickening in the breast tissue, changes to the skin covering the breast, such as dimpling, puckering, redness or scaling, changes to nipple, such as redness or scaling, or a nipple that begins to turn inward, and discharge from nipple [28].

7. Risk factors

Studies though indicate no clarity in the etiology of male breast cancer it is suspected that the hormonal levels have a role in its growth. The various risk factors include age, higher estrogen levels, BRCA gene mutations, and other [29]. Abnormalities like male infertility, orchitis, congenital inguinal hernia, undescended testes and also a history of breast trauma, discharges from the nipple, gynecomastia have been consistently shown to be associated with the disease [9]. Figure 6 shows a summary of risk factors of male breast cancer [30] and additional details of various risk factors are discussed below.

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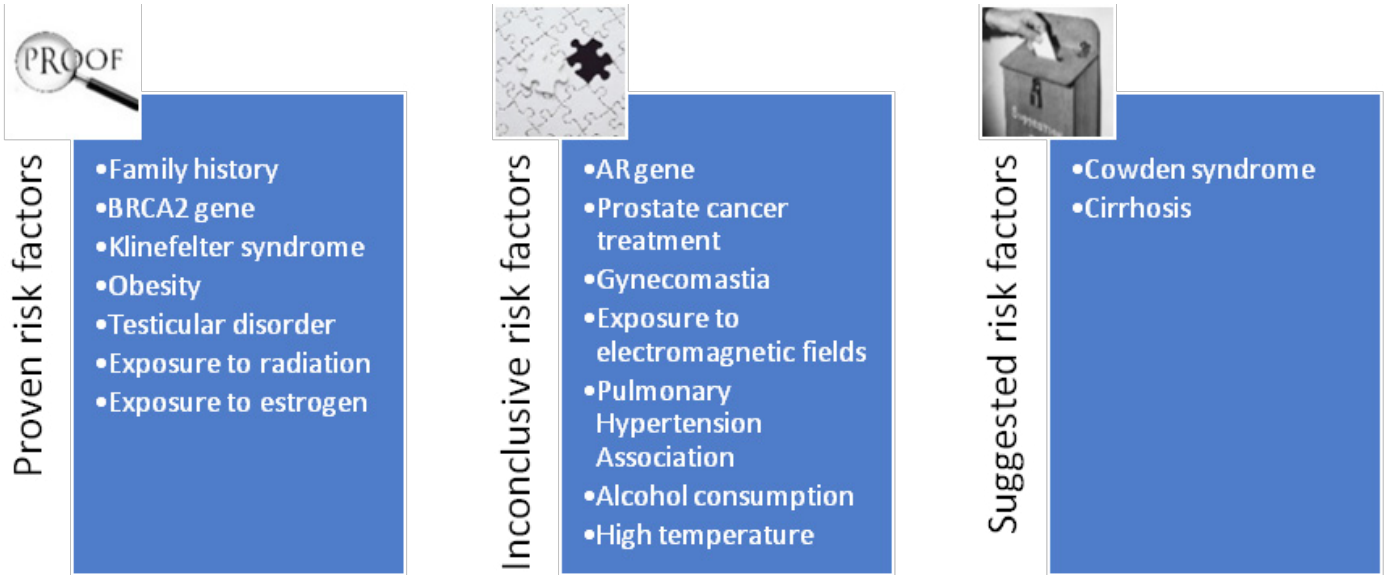

Figure 6. Risk factors of male breast cancer (Redrawn based on Table 1 in [30].

- **Older age:** The risk of breast cancer increases as the age increases. Male breast cancer is most often diagnosed in men in their 60s. In a study, the median age of patients during diagnosis of male breast cancer was 56 years (range, 22 - 78 years). Fifteen male patients (75%) were diagnosed after the age of 50 years and five were diagnosed before 50 years [31]. In the United States, men are 5 to 10 years older than women on average at the time of diagnosis of breast cancer [32].

- **Exposure to estrogen:** Exposure to estrogen may also increase risk of male breast cancer. High estrogen level is caused by one of the following factors: estrogen administration; occupational exposure to estrogen; estrogen containing creams or cosmetics; isoflavones; phytoestrogens containing cosmetics, soy products, beer, tea tree oil, lavender oil; estrogen action is caused by diethyl-stilbesterol, clomiphene, phenytoin, digitalis [33]. For example, if a person takes estrogen-related drugs, such as those used for hormone therapy for prostate cancer, he has increased risk of breast cancer [34].

- **Family history of breast cancer:** If a male having a strong family history of cancer, he has a greater chance of developing male breast cancer. A study in 1979 investigated the significance of family history in male breast cancer patients. Table 1 compares the eighteen male patients with multiple primary cancer and sixty-six male patients with no evidence of a second malignancy [35]. Patients with multiple primary cancers had a higher incidence of a positive family history of breast cancer (22%), positive family history of other cancers (38%), and appeared to be an older age group with a median age of 71 years at diagnosis of primary breast cancer. Research has identified several genetic variations associated with breast cancer risk. It shows that these genetic variations affect breast cancer risk in different ways for men and women. Researchers are finding how common gene variations may affect breast cancer risk. Each gene variant has only a modest effect on risk (10% to 20%), but when taken together they may possibly have a large impact [36].

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Details	Absence of multiple primary tumors	Presence of multiple primary tumors
Total No. of patients	66	18
Age at diagnosis of breast cancer		
Range	25-81	48-86
Median	61	71
Positive family history of breast cancer	10%	22%
Positive family history of other cancers	15%	38%
Positive family history of any cancer	26%	11%

Table 1. Comparison of Patients with or without Multiple Primary Tumours [35]

- **Klinefelter's syndrome:** Klinefelter's syndrome is a genetic syndrome occurs when boys are born with more than one copy of the X chromosome. Klinefelter's syndrome causes abnormal development of the testicles. As a result, men with this syndrome produce lower levels of certain male hormones (androgens) and more female hormones (estrogens) [36]. Klinefelter's syndrome as a risk factor for developing breast cancer was evaluated in a retrospective study of 93 unselected male breast cancer patients from the Healthcare region of Western Sweden. The prevalence rate of Klinefelter's syndrome in males with breast cancer was found to be 7.5%. Males with Cowden's disease Klinefelter's syndrome have a 50% greater risk of developing cancer compared to average healthy males [37].

- **Obesity:** Obesity is associated with higher levels of estrogen in the body, which increases the risk of male breast cancer. The association for obesity observed in men was of interest given a similar recognized pattern for female postmenopausal breast cancer [38]. In a study by pre-diagnostic serum/plasma samples showed that circulating oestradiol levels were associated with increased risk for male breast cancer. In obese men estrogen levels are high while testosterone and sex hormone binding globulin levels are low, resulting in higher bioavailability of estrogens and higher risk for male breast cancer. In addition, gynecomastia is a well-known risk factor for male breast cancer and is more common in obese men [38-40].

- **Testicle disease or surgery:** Testicular dysfunction and abnormalities have consistently been reported to be associated with an increased risk of breast cancer. A male having inflamed testicles (orchitis) or surgery to remove a testicle (orchiectomy) has increased risk of male breast cancer [30].

- **BRCA gene:** Similar to women BRCA1 and BRCA2 genes can undergo mutations/ abnormalities in men that are passed over generations. Malfunction of BRCA2 increase the risk of breast cancer by nearly 8 % and 7 times at risk with prostate cancer compared to men without the abnormal gene. Men with abnormal BRCA1 or BRCA2 genes are at a higher risk of developing skin and digestive track cancers [5]. It has also been reported that BRCA1 mutations in men may not be a common cause for cancer but 10%–16% of patients from high-risk families have BRCA1 mutations. Usually in majority of the cases low grade papillary and cribriform tumours are common while in situ ductal carcinoma is around 10% of breast cancers in men and in situ lobular carcinoma is rare due to absence of terminal lobules but has been reported in case of invasive lobular carcinoma [5]. There is some evidence indicating that CHEK2 creates predisposition to male breast cancer. A recent study reports that the growth hormones IGF-1 and IGF-2 naturally present in blood are also expressed by tumours of breast cancer [41].

8. Diagnosis and screening

Male breast cancer is rare and usually occurs later in men than women due to absence of basic awareness in male population leading to detection in advanced stages. Small lumps can be detected easily due to small volume of breast tissue but at the same time leads to accelerated spreading to the surrounding tissues. If detected during early stages, it responds appreciably to treatment and chances of survival for 5 or more years after diagnosis is high [42].

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Diagnosis of male breast cancer is generally delayed 6 to 10 months (the time from the onset of symptoms until the patient seeks treatment). This delay is partly due to

a) the rarity of the breast cancer in men
b) a lack of awareness and suspicion of the male breast cancer by patients and their doctors.

Because of this delay, a male present with the breast cancer at a later stage than women.

Stage I - ~40%
Stage II - ~20%
Stage III/IV - Over 40%

When breast cancer symptoms are present, triple test method is used to determine stage of cancer and the appropriate treatment plan. Triple test is the use of clinical exam, mammography or ultrasound, and fine needle aspiration or core needle biopsy. Mammography has been shown to have a sensitivity of 92% and a specificity of 90% in male breast cancer but is not used as a screening tool [43,44].

9. Treatment

Treatments differ by the stage of the cancer [43]. Early stage treatment involves cancers confined to the breast. Late stage treatment involves tumours that have spread beyond the breast. Treatments can include: surgery, radiation therapy, chemotherapy, hormone therapy, and targeted treatments. The process of detection, diagnosis, and treatment is similar to those of female breast cancer. Men diagnosed with male breast cancer at an early stage have a good chance for a cure. Once the disease has spread to the lymph nodes, which is more common among men, it requires more aggressive treatment and can increase the likelihood of developing a second cancer. Men who have had breast cancer have a higher risk for developing cancer in the opposite breast, melanoma and prostate cancer. Treatment typically involves surgery to remove the breast tissue. Other treatments, such as chemotherapy and radiation therapy, may be recommended based on specific situation. Treatment algorithm for advanced/ inoperable male breast is shown in Figure 7.

Mammography exhibits a sensitivity of 92% and specificity of 90% for male cancer diagnosis [5,45]. Ultrasonography can be used to get data on nodes. Biopsy of any suspicious mass identified by local imaging validate the diagnosis. Evaluation of estrogen and progesterone receptors; and her2-neu status to rule out any possibility that affect clinical management. The extent of disease can be determined from laboratory evaluation, bone scan, chest radiography, CAT scan of the abdomen deemed clinically appropriate [5].

The prognostic factors are tumour size and involvement of lymph nodes in males with breast cancer. It is reported that patients with tumours of 2–5 cm have a 40% higher death risk than with tumours of size less than 2cm and with involvement of lymph node the death risk is 50% more than without lymph node involvement [5,22].

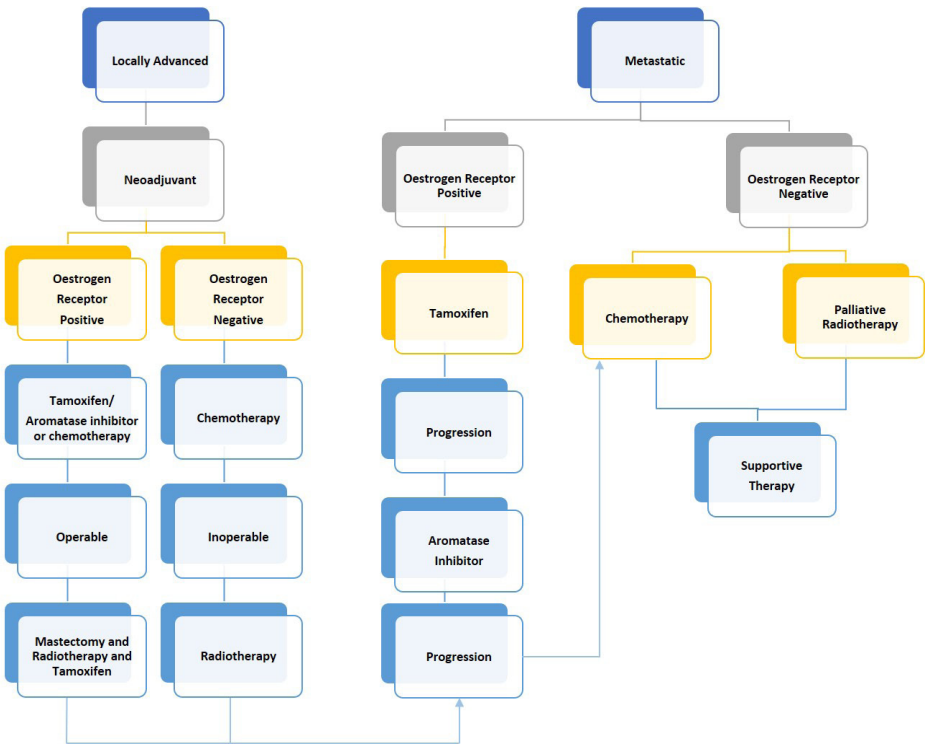

Figure 7. Treatment algorithm for advanced/inoperable male breast [43].

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9.1 Surgery

Simple mastectomy or modified radical mastectomy and surgical assessment of the lymph nodes are used when cancer is found in its early stages. Assessment of the lymph nodes is accomplished using either axillary dissection or sentinel lymph node biopsy. A study involved assessment of sentinel lymph node biopsy in 18 male breast cancer patients. 14 patients were followed up every 6 months (range 6–48 months) by clinical examination. There was no follow-up for the other 4 patients because of the short interval from surgery. No relapse, and neither local axillary recurrence nor distant metastases were discovered in any of the 14 patients. At the end of follow-up, no patients who had received sentinel node biopsy had axillary recurrences. One of these patients died because of an acute myocardial infarction; in another subject a prostate carcinoma was diagnosed [46]. Studies have reported that sentinel node biopsy is preferred if tumour is not fixed to pectoral muscle. Modified radical mastectomy with dissection of axillary lymph node is preferred to avoid recurrence. Studies conducted by Perkins et al. on 142 male patients treated at the University of Texas M. D. Anderson Cancer Center revealed that 18% of patients had relapse at chest wall and supraclavicular region, analysed with local regional failure predictors like number of axillary lymph nodes involved, tumour size and margin status [5].

9.2 Chemotherapy

Limited published data also support adjuvant chemotherapy in men with a projected 5-year survival rate of greater than 80% with reduced risk of recurrence [47]. Appropriate adjuvant chemotherapy based on the stage of the cancer and certain clinical indications is administered to improve the survival rate and reduce recurrence. Retrospective evaluation of adjuvant tamoxifen has indicated reduction in recurrence and death but needs extensive studies as it has been reported that men had lower drug tolerance with side effects like mood alterations, decreased libido, deep-vein thrombosis, impotency, increased risk of blood clots, bone thinning, hair loss, hot flashes, muscle and joint pain [48]. Appropriate adjuvant chemotherapy based on the stage of the cancer and certain clinical indications is administered to improve the survival rate and reduce recurrence. Role of aromatase inhibitors in adjuvant therapy for male patients is limited and needs further investigation to substantiate its efficacy [49].

9.3 Radiation therapy

Patients with male breast cancer tend to be diagnosed with larger tumour, probably due to the fact that males present with breast cancer at a later stage than females. Males are more likely to receive radiotherapy than females because male breast cancer are diagnosed at later stages. Radiation dosages used to treat men are generally the standard amounts used to treat women. Radiotherapy has been shown effective in preventing local recurrence in men with breast cancer [50]. Male patients undergo radiation therapy after mastectomy due to involvement of nipple or skin and prevents any local recurrences. In cases of post mastectomy of large tumour size greater than 3cm, radiotherapy is preferred to prevent local recurrence, but adequate data is not available to have a better understanding of the overall survival rate.

9.4 Immunotherapy

Recent studies in a few types of cancer have shown a promising new way to get immune cells called T cells (a type of white blood cell) to fight cancer by changing them in the lab so they can find and destroy cancer cells. Research for this type of treatment in breast cancer is being investigated [51].

9.5 Hormone Therapy

Because about 80% of men with breast cancer are estrogen receptor positive (ER+), treatment with tamoxifen is standard in ER+ men. Men treated with tamoxifen have shown higher overall survival rates. Men may also receive systemic chemotherapy. Tamoxifen had minimal side effects and it does not produce any severe marrow toxicity [52].

9.6 Electrochemotherapy

A study involving 12 patients (1 male and 11 females, median age of 76 years) with regional or distant skin or subcutaneous metastases from breast cancer, with or without visceral disease was done using electrochemotherapy (ECT). They observed complete response in 75.3% (107 metastases), partial response in 17% (24 metastases), no change in 7.7% (11 metastases). No serious ECT-related adverse events were reported; adverse events consisted of pain in the treated area one to two days after treatment (1 patient, 8.3%) and ulceration of treated area (1 patient, 8.3%). ECT could be suggested as a primary local therapy in breast cancer patients not suitable for surgical removal of the primary tumour, and clinicians should not hesitate to use it even in the elderly [53]. Table 2 gives the details, which are coupled for both male and female patients, with respect to the treatment and its response.

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Parameter	Details
Case Subject	One Elderly Male Patient (out of total 12 patient)
Age Group	Median age of 76 years
Ailment	Reginal or distant skin or subcutaneous metastases from Breast Cancer
Study Timeline	March 2010 to October 2011
Procedure	Bleomycin (15.000 IU/m2) followed by Electrical Pulse to each tumor nodule.
Electrical Pulse	Within 8 min after Intravenous Infusion of the drug
Needle Electrode	2-3 cm based on the lesion size.
Electroporation Device	Cliniporator™ Device
Findings	In intricate cases where surgical removal of breast cancer is not reasonable, especially in reasonably aged patients, ECT possesses the potential of being supported for treatment.

Table 2. Electrochemotherapy of male and female breast cancer patients' data

In another case in the UK, a lump was discovered on a male patient's chest in early 2008 and mastectomy was performed. However, in summer 2010, he found several small lumps under his arm-the cancer had returned in the form of skin cancer. This was treated using electrochemotherapy successfully, eradicating most of it [54].

9.7 Proteomics Studies

Zografos, et al. [55] reported proteomic data related to the differential serum protein expression profile in men with breast cancer in contrast to their healthy counterparts. It presents the possibility of identifying potential biomarkers to combat male breast cancer and advocates a more personalized approach for treatment. There were 11 MBC patients and eight healthy individuals. They performed 2D GEL Electrophoresis studies of the serum and identified a total 42 proteins, of which, 38 were common for both groups and four were only found in MBC group. These data could be used for personalized therapy for MBC patients. Table 3 presents the details of this study.

Camarillo I, Thulasidas JS, Kalavathy G, Poompavai S, Giri P, Sahu P, et al. Male Breast Cancer: Another look. G Med Sci. 2021; 2(2): 015-029.
https://www.doi.org/10.46766/thegms.oncol.21040502

Parameter	Details	
Subject	Eleven (11) Male Patients	
Age Group	≤ 50 Years	2 (18.2%)
	≥ 50 Years	9 (81.8%)
Race	Caucasian	11(100%)
Ailment	Breast Cancer	
Receptor	ER +ve	10 (90.9%)
	ER –ve	1(9.1%)
	PR +ve	9 (81.9%)
	PR -ve	1(9.1%)
	HER2/new +ve	1 (9.1%)
	HER2/new -ve	10(90.9%)
Control Group	Eight (8) Healthy Individual	
Age Group	Age-Matched with MBC patients	
Sample Used for analysis	Blood Serum	
Methods for Analysis	Proteomics Analysis- 2D Gel Electrophoresis	
	Mass Spectroscopy - Protein Identification by MALDI-TOF-MS	
	Enzyme-linked Immunosorbent Assay (ELISA)	
	Western Blot Analysis	
	Pathway Analysis using STRING and PANTHER.	
Four Specific Protein in MBC patient (not found in control group)	1. Actin-related protein 2/3 complex subunit 4 (ARPC4) 2. Dual specificity mitogen-activated protein kinase kinase 4 (MAP2K4) 3. Ectoderm-neural cortex protein 1 (ENC1) 4. Matrix Metalloproteinase-27 (MMP27)	
Partial list of proteins common to both groups	ANCHR, ALDH2, STAT3, CDC7, CYP19A1, CD5L, MLH3	

Table 3. Data of MBC patients and healthy individuals.

Part of the 38 commonly expressed proteins in the serum of MBC patients were used to generate String Interaction diagram [56]. Figure 8 shows the interactions between various proteins. It is identified that STAT3 gene, which is responsible for activation of all forms of breast cancer and aids in tumour growth and metastasis has strong interactions with Tripartite motif-containing 28 (TRIM28) and CRYAB gene. CRYAB is categorised under heat shock protein family. These are molecular chaperones, which aid in folding and unfolding of macromolecular structures that contributes in stabilizing the malignant overexpressed oncoproteins found in breast cancer cells [57], which also inhibit apoptosis.

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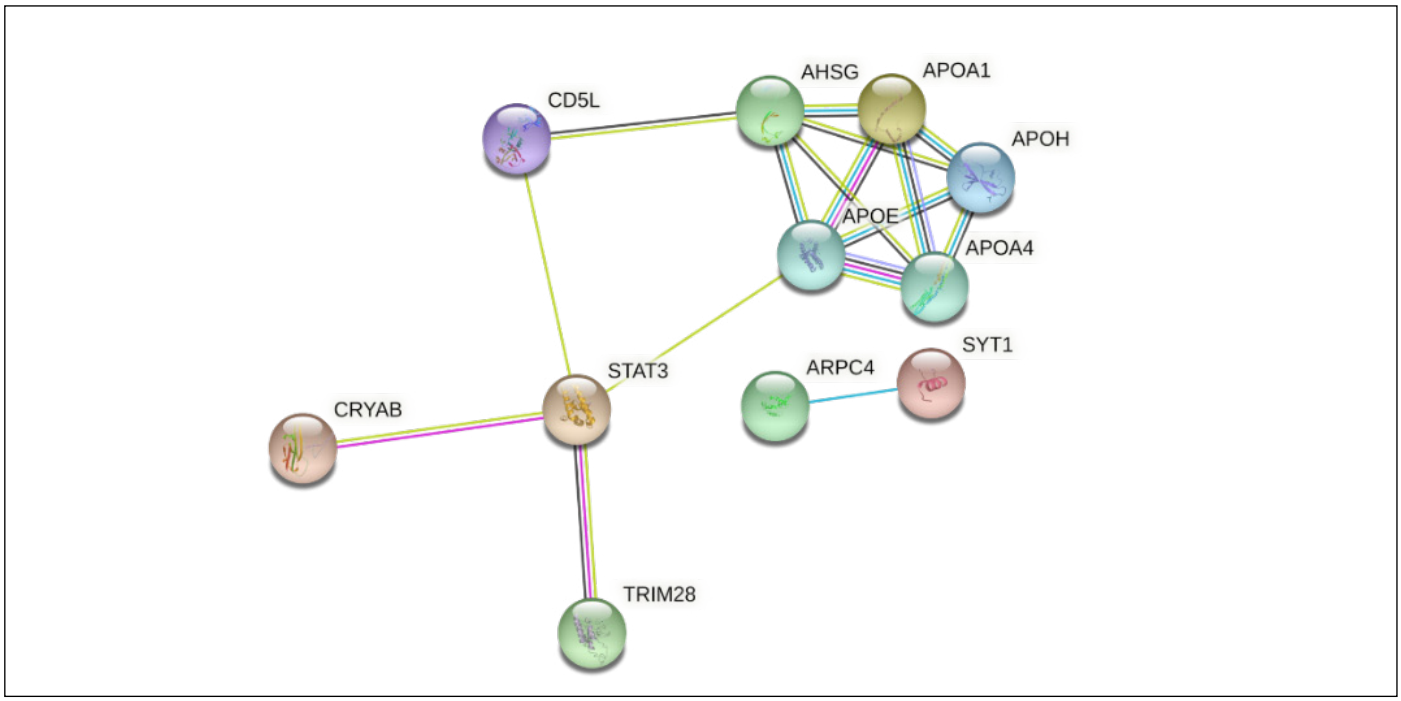

Figure 8. Protein-Protein Interactions of the common proteins.

10. Conclusion

Male breast cancer, although uncommon, is increasing, similar to female cancer. Male and female breast cancers though similar with respect to epidemiological aspects, MBC differs widely in terms of very low incidence and late onset. Pathogenesis of both male and female breast cancer involve environmental, hormonal and genetic factors while insignificant data available on male cancer etiology. Cancer cases in the family is a huge risk factor in males as they are highly susceptible due to rare mutations in high-penetrance genes, while low-penetrance genes contribute to increase in lower risk. The distinct features of male breast cancer must be utilized for their treatment. Current efforts at pooling epidemiologic data, clinical information, and tumor specimens will lead to a greater understanding of the etiology of this disease. Education of both patients (and doctors) is needed to increase awareness of male breast cancer, to guide evidence-based treatment, and to encourage enrolment onto future clinical and biologic studies aimed at optimizing treatment for this rare disease. Future studies with a focus on biology and protein profiles and genomics of the male breast cancer are crucial to advance the understanding of the disease and to optimize the care of all male patients. Support systems for men with breast cancer are rudimentary and need more resources and research at a national rather than a local level.

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