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COMMENTARY

# Breast Cancer in Men

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## Introduction

Breast cancer is the rapid growth and division of cells in the breast's anatomy [1]. It's well-known and well-studied because of its common occurrence and high incidence in women [2]. Estimates made by the National Cancer Institute show that breast cancer is the most frequently diagnosed cancer in the United States in 2022[3]. However, it's unknown to many that men can also develop breast cancer [4]. While cases are rare, its presentation and prognosis in men, the development of the disease, the genetic mutations that show higher risk of breast cancer in one sex over the other, and slight but notable differences in the pathophysiology of male breast cancer compared to female breast cancer are topics worthy of discussion and further study [5].

Male breast cancer is a relatively misunderstood and understudied disease due to its rarity in the sex [6]. Less than 1% of all breast cancers are found in men, and less than 1% of all cancers found in men are breast cancers [7]. Still, the disease is a serious topic worthy of discussion as rates of male breast cancer have steadily risen each year all across the globe [8]. This may be in part due to risk factors such as obesity and hormonal imbalances being more prevalent in the present day [9]. Additionally, genetic mutations such as BRCA1 and BRCA2 can predispose some men to develop male breast cancer, and are more likely to develop the disease if they have a blood relative who has developed breast cancer [10]. Most men do not properly screen themselves for the disease and most are completely unaware of what symptoms of the condition may present as. This leads to diagnosis at later stages of the disease [11, 12]. Stigmatization also plays a role in delayed diagnosis and treatment leading to a significantly higher mortality rate when diagnosed with breast cancer than women [13-16]. Unfortunately, because of the rarity of the disease and its lack of understanding even in the medical community, primary care providers and other physicians who are unaware of how to recognize, manage, or treat male breast cancer may delay treatment or refer patients to another doctor who is inexperienced in diagnosing the disease [17]. More research on the disease in men is needed and awareness should be raised in the community and medical field.

## Prognosis

Since male breast cancer is found in less than 1% of any type of cancers in men and less than 1% in breast cancer in the Unites of States, there is little information about its etiology. A research study that investigated the differences between men and women in regards to mortality and survival rates in breast cancer found that breast cancer in men is diagnosed in a higher stage than in women, since it is detected later

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on [18]. Unlike women, screening allows for breast cancer to be detected and treated earlier than it is for men.

There are 2 main subtypes, one being the complex subtype which seems to be similar to the female luminal breast cancer. Then there's the male simplex subtype that does not exist in female breast cancer. Breast tissue consists of milk-producing glands (lobules), ducts that carry milk to the nipples, and fat [10]. During puberty, women begin developing more breast tissue, and men do not. But because men are born with a small amount of breast tissue, they can develop breast cancer. If men have been diagnosed with breast cancer, they might need more tests to see if the cancer might have spread [19].

Some possible symptoms of breast cancer in males include lumps or masses in the breast area. However, it's important not to rely on these alone. You should also see your doctor if you notice any unusual changes in size, shape and feel of one or both of your breasts. It's important to remember that the symptoms of breast cancer in males aren't the same as those of women. Knowing the common symptoms can help you get early treatment and make sure that you're getting regular checkups from your doctor. As we know, BC in males is quite rare. However, there are several explanations that may help men understand how breast cancer can happen in men. We have age, overall health, estrogen levels, family history, genes, radiation therapy, and testicular issues [20].

First of all, those men who are 60 years or older are more likely to develop breast cancer. It is not common for men to experience gynecomastia. However, a condition known as gynecomastia is a condition that occurs in a few men, that is an enlargement of the male breast gland or fat tissue in the chest area. If you have a first degree relative (mother, sister, or daughter) with BC, you have an increased risk of developing the disease yourself. Estrogen is a hormone produced by the ovaries. Certain drugs, cirrhosis and Klinefelter syndrome increase estrogen levels, increasing the risks of several health problems, including BC. Scientists have identified several genes that affect your risk of developing breast cancer. These include changes in the BRCA1 and BRCA2 genes. Those who have had radiation therapy in the chest or torso, have a higher risk of developing BC. Last but not least, the removal of the testicles increases a man's risk of breast cancer because he does not produce testosterone. Testicle injuries also increase the risk [21].

## Prevalence

According to the American Cancer Society, 2,700 men are diagnosed with breast cancer, meaning one in every 833 men will be victims and nearly 530 die from the disease [22]. This is actually less than one percent of male population and much lower than the rate of breast cancer in women, making it very easy to ignore. However, male breast cancer has been proven to be more prevalent depending on race. It has been shown to be higher in non-Hispanic black races and whites [23]. They are 1.2-1.5 times more likely to get diagnosed with breast cancer. Another main factor is age. Even though it is a disease that is present in all ages, it is much more common in individuals who are 60+ years old. Mortality rates also increase with age, but most cases are treated while in stage II [24].

In addition, location also seems to play a significant role. It has been shown to be more common in metro areas, according to the national cancer database [25]. In fact, numbers in metro areas are larger than rural and urban populations combined. This especially applies to east and central regions rather than western ones. In the past years, this disease has been shown to increase in both male and females. Over the last 10 years, the rate has gone from 7% to 10.3 % [26]. The good news is that, although breast cancer in men is gaining more prevalence, death rates have remained low and are progressively decreasing.

## Risk Factors

Proneness to breast cancer amongst men starts increasing at the age of 50. Risk factors include genetic mutation, family history of breast cancer, exposure to estrogen, alcohol, liver disease, Klinefelter's syndrome, testicle disease or surgery [27]. There is a current lack of awareness regarding the role of obesity in male breast cancer. Men with a 35% high BMI have a greater risk than men with a low BMI [28]. Table 1 includes risk factors for male breast cancer.

## Genetics

Genetics dictate all physical characteristics within all living organisms including, predisposition to diseases, allergies and mutations. Male breast cancer (MBC) is no different. Modern technology such as polymerase chain reaction (PCR), gene probes, oligonucleotide arrays, microchips and next-generation sequencing technologies permit us to analyze genes and their roles within the body such as,

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susceptibility to certain conditions [30]. If the patient has a positive family history from MBC, then the genetic likelihood for them contracting is increased compared to another man with a negative family history with 10% of all MBC cases caused by inherited gremlin mutations. Genes are classified as high-penetrance, moderate-penetrance and low-penetrance. Genes known to increase likelihood for developing MBC include BRCA1 & BRCA2 as high penetrance, the level of penetrance of a gene is determined by the rate of mutation and magnitude of impact. Known high penetrance genes involved in MBC include BRCA1 and BRCA2 which when mutated point at a high risk to developing MBC whilst variants of the genes can have a <5% moderate risk factor and CHEK 2 & PALB2. With recent findings pointing at a low-penetrance group of MBC susceptible alleles but their low penetrance leaves ambiguity in their direct correlation to breast cancer [31]. Table 2 outlines the classes of male breast cancer genetic susceptibility and comparison of their different features and Figure 1 shows the regularity of gene mutations in MBC tumors.

## Treatments

There are different ways breast cancer in men can be treated, it can be as simple as taking medication to as complicated as needing radiation. Treatments in male and female breast cancer are similar but most male patients will undergo radiation therapy and mastectomy, while female patients most commonly partake in chemotherapy and lumpectomy [33]. Male and female treatments involve: surgery, chemotherapy, radiation therapy, hormone therapy, and targeted therapy [34]. Surgery, in surgery treatment there are two main types: lumpectomy and mastectomy [35]. A lumpectomy surgery removes the tumor and small parts of normal tissue; while a mastectomy surgery removes the whole breast which may include part of the skin, nipple, areola, and lymph nodes. Chemotherapy, chemotherapy is a treatment that can be taken by pill or injection, the drug helps prevent growth of more cancer cells by either stopping the cells from dividing or killing them. Hormone therapy, hormone therapy is a treatment that is used only for hormone sensitive cancers, it stops hormones or blocks hormone receptors from attaching to cancer cells to prevent or decrease the production of hormones [36]. Radiation therapy, radiation therapy is a treatment that involves high energy x-rays and radiation to kill or keep cancer cells from growing. There are two types of radiation therapy: external and internal radiation. External radiation uses a machine that delivers radiation outside the body towards the cancerous area and internal radiation is a device that is temporarily placed on the cancerous area after surgery [37]. Targeted therapy, targeted therapy causes the least amount of harm to normal cells then other breast cancer treatments, this treatment uses drugs to identify specific cancer cells and attack protein that makes cancer cells grow in an abnormal way [38]. Clinical trials, clinical trials are a type of research study that helps improve ongoing treatments or collect information to help with new treatments. For many patients, clinical trials are the best treatment option. Some trials use patients that have yet to be treated and others whose cancer has not improved. Clinical trials are starting to take place all over the country helping to determine how cancer will get treated in the future. However, risk of having breast cancer and going through treatment can be reduced by keeping a healthy weight and exercising regularly.

## Awareness

Since breast cancer in males is not as prevalent within the population, there is a lack of awareness that contributes to many late diagnoses [39]. A majority of 81% of men that have been diagnosed were not aware of the presence of their illness, while only 19% of men were aware that they had cancer [40]. These statistics occurred as a result of the lack of knowledge provided about the sickness and the symptoms that can occur. Depending on the growth of the cancerous cells, it can be easier to detect breast cancer in men if the growth is around the mammary papilla because the abnormal lumps would be more visible compared to those found in women [41]. However, since men's breast tissue is smaller in mass, the possibility of the cancerous cells multiplying behind the teat can increase the potential of being diagnosed late. While women have yearly checkups and a screening process with their physicians to make sure that these abnormalities are not occurring within the breast, males have no sort of confirmation to provide reassurance that they themselves are not developing abnormalities [42]. This information is extremely important to know to help the prevention of growth, but yet not many males are provided this information, and as a result, many lives are lost. Learning about breast cancer in men can reduce the risk of late diagnosis and help provide treatment in the early stages of development. By raising awareness and improving the educational process in which we inform males about the possibility of breast cancer, we can eliminate the social stigma of breast cancer in men, and prevent the progression of cancer development, helping to save many lives.

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## The Stigma: A Woman's Disease in Men

When the general population fears a diagnosis, namely cancer, it tends to become a stigma in society. Stigmatization can lead to becoming isolated and excluded socially via loss of employment which can lead to loss of household and social status. A newly diagnosed male having what is traditionally misconceived as "a woman's disease" can end up with a negatively impacted sense of self identity. Emasculation is also a likely result of a male breast cancer (MBC) diagnosis [43]. Another factor that promulgates the stigma is sexism. Breast cancer screening is established in preventive medicine care for female patients, while prostate cancer screening is the preventive medicine focus for male patients [44]. In a qualitative study on MBC for participants ages 53-83, the participants expressed uncertainty in using tamoxifen for their hormone treatment. They felt there should be a need to study the effectiveness of the hormone based drug in males. Furthermore, there are many advertisements for solutions to chemotherapy induced problems with respect to body image such as the use of special bras and breast implants, and hair replacement for females, but not for males [45, 46]. Hair loss and alopecia due to chemotherapy are issues that cause distress in both males and females. Yet, very few academic or medical journal articles can be found on the topic of male alopecia due to MBC treatment. Study results reveal that males are not able to hide hair loss, and females have more tools available to decrease the appearance of hair loss. Also, males tend to make jokes to hide insecurities caused by hair loss [47]. Healthcare providers need to better understand the underlying of how patients deal with MBC as compared to females in order to better address their social and psychological needs. By anticipating MBC patients' emotional, psychological and physical needs, the effects of stigmatization may be minimized.

## Survival Rate

If you haven't been diagnosed with male breast cancer and you have a BRCA1 or BRCA2 mutation, your doctors may recommend that you receive periodic screenings for breast cancer and other cancers [48]. The 5-year survival rate for men with breast cancer is 84%. The survival rate depends on different factors, including the stage of disease when it is first diagnosed. Study shows that about 47% of cases are diagnosed at this localized stage. It is important to remember that statistics on the survival rate for men with breast cancer are at an estimate. The estimate comes from annual data based on the number of men with this cancer in the United States. Also, experts measure the survival statistics every 5 years. This means the estimate may not reflect the results of advancements in how men with breast cancer are diagnosed or treated from the last 5 years. Even if the cancer is found at the most advanced stage, new treatments help many people with breast cancer maintain a good quality of life for some time. Also it varies on how you respond to the treatment, and depends on how healthy you were before having breast cancer. Survival rates can describe any length of given time. However, researchers usually give cancer statistics as a 5-year relative survival rate. There is a 5-year survival rate for men, the 5-year survival rate for men is 84%. There are different types of cancer so it depends what type of cancer you have to know the survival rate. The most common breast cancer found in men is the same kind found in women. Survival statistics also help doctors evaluate treatment options. Depending on where the cancer spreads, for example if it spreads to a distant part of the body the 5-year survival rate would be 22%. These epidemiologic factors, in addition to studies suggesting that men with breast cancer have elevated estriol production, indicate a relationship between male breast cancer and hormones in addition to the well-established relationship with genetics [49]. It depends on the type of cancer men have and some can have a lower chance of survival rate. The stage of cancer, because sometimes it is worse, for example it could be stage 5 or 1. How you respond to the treatment is also very important. Our body's respond differently to the treatment. Your age and how healthy you were before cancer helps a lot and most likely shows how you are going to react to the treatment. Treatment and management of male breast cancer typically follow the same rationale of breast cancer in females, which consists of resection followed by adjuvant endocrine therapy, chemotherapy (CT), or radiotherapy [27]. Many people do not realize that men have breast tissue and that they can develop breast cancer. The cells in our body can become cancer and can spread to other areas. If you haven't been diagnosed with male breast cancer and you have a BRCA1 or BRCA2 mutation, your doctors may recommend that you receive periodic screenings for breast cancer and other cancers.

## Conclusion

Although breast cancer is one of the least common types of cancer amongst males, risk is still present. With approximately 530 deaths a year and a mortality rate of 0.29%, the uncommonness of the disease does not invalidate its risk of mortality [13,22]. Furthermore, current statistics regarding male breast cancer are not believed to accurately encompass reality due to the lack of awareness and societal

discredit (neglection) within the male population. This causes a vast amount of undiagnosed patients to go unseen or be diagnosed at a late stage contributing to less than 1% of breast cancers diagnosed in men [50]. The low prevalence complicates any further studies on the psychosocial effects of the disease in men, pathophysiological differences in men and women, and the causes behind higher mortality rates.

Although little research has been conducted regarding the effects of treatment on males with MBC, a recent survey found worse mental and physical health in breast cancer survivors [51]. Poorer mental, physical, and emotional health was correlated with obesity, diabetes, and activity limitations in patients with MBC [52]. With MBC being primarily hormone receptor positive, including the androgen receptor (AR) and prevalence of BRCA2 germline mutation, female breast cancer and MBC are different molecularly (different gene mutations and subtypes) and in histology [10]. Due to inadequate research in men, diagnosis and treatments are shy of current scientific advancements available to women [5]. MBC survival rates are overall 4.6 % lower than that of female breast cancer patients [26]. Despite biological differences, current treatments for males are mostly based on studies done in women [53]. However, discovery and application of different treatments such as poly-ADP-ribosome polymerase (PARP) inhibitors, sex-steroid biosynthesis pathway, and AR activation (targeted agents) are promising for the treatment of MBC [10]. As the rate of MBC incidence increases yearly, global cooperation and further research is imperative for the further advancement of treatment and awareness [26]. There is evidence that spreading awareness amongst patients and medical professionals leads to an increase in early-stage detection leading to overall and disease-free survival [10, 26]. There is an opportunity to develop education and awareness campaigns and research done on the disease as a whole, making it easier to inform the public and healthcare providers on how to properly diagnose, manage, and treat breast cancer in men.

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**Table 1: Risk Factors for Male Breast Cancer**

| **Strong Risk Factors** | **Moderate Risk Factors** | **Weak Risk Factors** |
|---|---|---|
| *Family history of breast cancer.* Having breast cancer family members increases the risk of developing this disease.<br><br>*Genetic mutation*. Men who inherit BRCA2 have a 6% greater risk of breast cancer<br><br>*Liver disease*. Male breast cancer risk increases as scarring of the liver lowers androgen levels and raises estrogen levels.<br><br>*Testicle disease or surgery*. Having orchitis, an injury, swelling, or surgery to remove a testicle has a higher risk of breast cancer.<br><br>*Klinefelter's syndrome*. A rare genetic condition that has caused the male to have an extra X chromosome.<br><br>*Exposure to estrogen.* Hormone therapy for prostate cancer can increase your risk of breast cancer | *Older age.* As you get older the risk of having breast cancer increases. Male breast cancer is often diagnosed in their early 60s.<br><br>*Radiation therapy treatment.* Men who are treated for cancer in the chest may be at increased risk of developing breast cancer. The hormonal changes that occur after radiation treatment in men can cause abnormalities in breast tissue<br><br>*Obesity.* Men who have obesity or are overweight are mostly likely to get breast cancer | *Hormone therapy treatment.* Prostate cancer treatment with drugs containing estrogen increases men's breast cancer risk.<br><br>*Alcohol*. Drinking alcohol is linked to an increased risk of breast cancer. This may be due to the effects of heavy drinking on the liver, which can influence how Hormone receptors work in the body. |

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**Table 2: Classes of male breast cancer genetic susceptibility and comparison of their different features**

| | **High Penetrance** | **Moderate Penetrance** | **Low Penetrance** |
|---|---|---|---|
| **Genes** | *BRCA2, BRCA1* | *CHEK2, PALB2* | 2q35, 6q25.1 (*ESR1*), 10q21.2, 11q13.3, 12p11.22, 14q24 (*RAD51L1*) and 16q12.1 (*TOX3*) |
| **Population frequency** | <0.1% | MAF 1% | MAF >10% |
| **Cancer risk (odds ratio)** | >10.0 | >2.0 | 0.76–1.57 |
| **Functional effect** | Direct effect of mutation | Direct effect of variant | Direct effect of variant; linkage disequilibrium with causal variants |
| **Strategy for identification** | Resequencing of candidate genes | Resequencing of candidate genes | Case–control studies; genome-wide association study (GWAS) |

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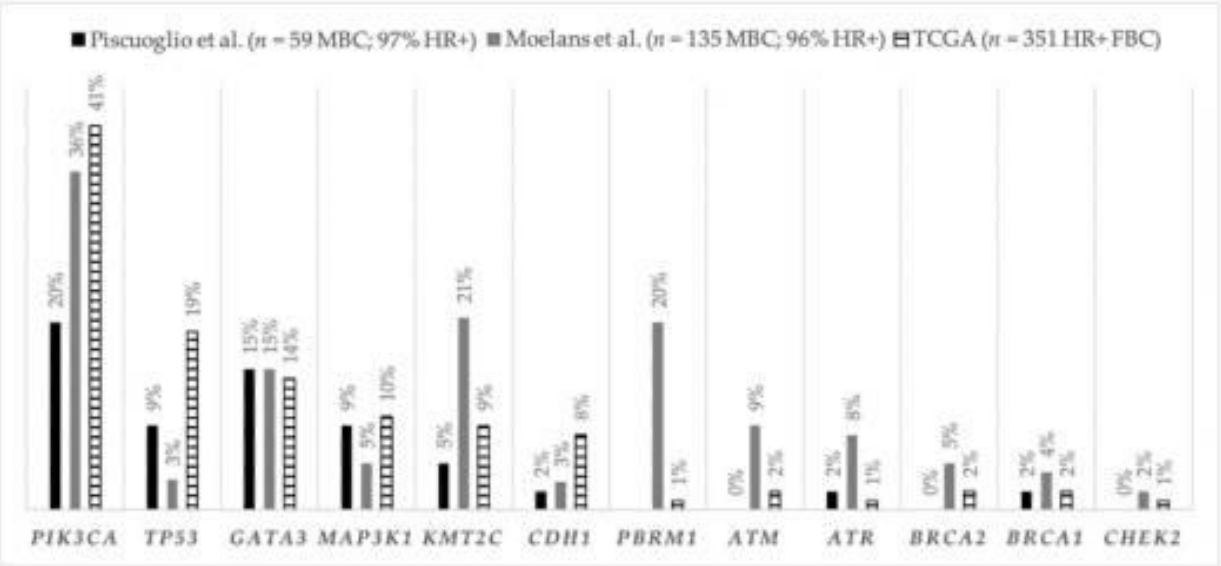


**Figure 1. Regularity of gene mutations in MBC tumors and BC (Breast Cancer) and The Cancer Genome Atlas genetics program (TCGA) samples**

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