Males at High Risk for Breast Cancer: Who Are They and How Should We Screen Them?

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Abstract

Background: It is estimated that 2240 males in the United States will develop invasive breast cancer (BC) in 2013, resulting in 410 deaths. Overall, male breast cancers (MBCs) are diagnosed with larger tumor size, more frequent lymphatic invasion, and advanced tumor stage compared to their female counterparts. Several risk factors have been elucidated for the development of MBC, and this paper aims to critically review the existing literature on at-risk populations and provide screening recommendations. Methods: A comprehensive search for all published studies on populations at risk for MBC using PubMed, EBSCOhost, and Google Scholar was performed (1982-2013). The search focused specifically on genetic and epidemiologic risk factors, and screening for MBC. Keywords searched included “male breast cancer risk factors”, “male breast cancer epidemiology”, and “male breast cancer genetics”. A total of 34 studies involving 4,865,819 patients were identified. Results: Five studies (N = 327,667) focused primarily on family history of breast cancer as a risk factor for MBC. 15% - 20% of men with BC have a family history of breast or ovarian cancer, and a family history of BC among first-degree relatives confers a 2- to 3-fold increase in MBC risk (odds ratio = 3.3). Seventeen studies (N = 5451) analyzed associations between several heritable genes and MBC. Lifetime MBC risk among BRCA1 mutation carriers is 1% - 5%, while MBC risk in BRCA2 mutation carriers is higher and varies between 4% - 40%. Less clear associations between MBC and PALB2, Androgen Receptor gene, CYP17, and CHEK2 mutations have also been documented. Five studies (N = 16,667) have addressed occupational risk factors for MBC. An 8-fold increase in MBC is reported in males working in the cosmetic cream manufacturing, and the motor vehicle industries. A meta-analysis of 18 trials also identified electromagnetic field exposure as a potential MBC risk, though causation remains undocumented. Eleven studies (N = 4,843,598) analyzed the role of abnormalities in the androgen-to-estrogen ratio as a risk factor for MBC. Conditions associated with increased MBC risk include Klinefelter’s syndrome (relative risk, RR = 29.64), obesity (RR = 1.98), orchitis/epididymitis (RR = 1.84), and gynecomastia (RR = 5.86). Conclusion:

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Routine screening for MBC should be considered in all high risk male populations, including those with a prior history of breast carcinoma, a strong family history of BC (defined as an affected mother or sister), a positive BRCA2 mutation status (regardless of family history), and men diagnosed with Klinefelter's syndrome, or those in the chemical or motor vehicle industries. Genetic testing for BRCA2 should be recommended for all MBC patients. Increased public and physician education on MBC is necessary to raise awareness about this rare disease and the need for screening of at-risk populations.

Keywords
Male Breast Cancer Risk Factors, Carcinoma of the Male Breast, Breast Carcinoma

1. Introduction
The American Cancer Society (ACS) estimated there will be 2240 new cases of male breast cancer (MBC) in the United States in 2013, and ~410 males will die from this disease [1]. The Surveillance, Epidemiology, and End Results registry has recorded 5494 cases of MBC between 1973 through 2005, with a median age at diagnosis of ~67 years, and an age-specific incidence rate demonstrating a single peak age at ~75 years [2]. Male breast cancers are typically diagnosed with greater tumor size, more frequent lymphatic involvement, and advanced tumor stage compared to females, which is at least in part the result of no defined screening programs for at-risk males and almost no public education on this topic [2] [3]. Given the rarity of MBC, large-scale familial, genetic, and environmental epidemiologic studies have proven difficult to conduct. This paper critically examines the existing literature on male populations at high risk for breast cancer, and provides specific screening recommendations for these populations.

2. Methods
A comprehensive search of all published studies addressing populations at risk for male breast cancer was conducted using PubMed, EBSCOhost, and Google Scholar (1982-2013). The search focused specifically on genetic and epidemiologic risk factors for male breast cancer. Keywords searched included “male breast cancer risk factors”, “male breast cancer epidemiology”, and “male breast cancer genetics”. A total of 34 studies involving 4,865,819 patients were identified. Inclusion criteria for studies included those focusing on epidemiological considerations including age, ethnicity, socioeconomic status, and occupation, as well as more traditional risk factors such as ethnicity, family history, BRCA/other genetic mutations, and genetic syndromes.

3. Family History of Breast Cancer
Five studies involving 327,667 patients (Table 1) addressed the impact of positive family history on MBC. It has been estimated that 15% - 20% of all MBC patients have a family history of breast cancer, with at least one first- or second-degree relative affected by the disease [4] [5]. In an analysis of gremlin mutations in 34 MBC patients, Haraldsson et al. found a positive family history of breast cancer in 13% of MBC cases [6]. Brinton et al. conducted a prospective cohort study of 324,920 men in the National Institute of Health-AARP Diet and Health Study, of which 121 developed breast cancer (9 with in situ disease, 107 with invasive breast cancer, and 5 with unknown stage) [7]. The authors found an increased risk of breast cancer among men who reported breast cancer in a first-degree relative (RR = 1.92, 95% CI: 1.19 - 3.09), and that risk was particularly increased for individuals with an affected sister (RR = 2.25, 95% CI: 1.13 - 4.47), or both an affected mother and affected sister (RR = 9.73, 95% CI: 3.96 - 23.96) [7]. Similarly, in a population-based case-control of 81 MBC cases and 1905 male controls, Johnson et al. reported an increased risk in males with an affected mother or sister (OR = 3.65, 95% CI: 1.62 - 8.19) [8]. In a case-control study including 21 MBC cases and 82 controls, D’Avanzo et al. reported that a positive breast cancer family history in a female relative was associated with an increased risk of MBC, and an odds ratio of 8.5 (95% CI: 1.1 - 69.0) [9]. Those results were confirmed by Ewertz et al. who conducted a population-based case-control study including 156 MBC patients and 468 controls and calculated an odds ratio of 3.3 (95% CI: 2.0 - 5.6) for males with a positive family history of breast cancer [10].
4. Genetic Mutations

Seventeen studies involving a total of 5451 patients (Table 2) analyzed the associations between heritable genetic mutations and the development of MBC. Identified cancer susceptible genes include BRCA1/2, PALB2, AR gene, and CHEK2 mutations, as well as CYP17 promoter polymorphisms [3] [4] [6] [11]-[24].

4.1. BRCA Gene Mutations

The BRCA genes are classified as tumor-suppressor genes, in that they maintain genomic stability and cell-cycle checkpoint control [25]. Mutations in the BRCA1/2 genes results in cancer initiation, and the subsequent accumulation of genetic mutations and instabilities can ultimately engender cancer development [25]. The reported frequencies of BRCA2 germ-line mutations in MBC vary between populations, likely due to small sample sizes and varying methodologies and sensitivities of mutation screening methods [24]. Friedman et al. analyzed 54 cases of MBC from a Southern-California population and identified only 2 (4%) carriers [4]. Contrarily, Thorlacius et al. [11] reported that 40% of all MBC cases diagnosed in Iceland over a period of 40 years carried a specific BRCA2 mutation (999del5), and Couch et al. [12] reported a 14% mutation rate in their study of 50 MBC patients. Mavraki et al. screened DNA from 26 males affected with breast cancer, and identified 3 pathogenic mutations, all of which resulted in premature termination of translation, and calculated a 7% - 11% frequency of BRCA2 germ-line mutations [17]. In a population-based study of 94 MBC cases, Basham et al. identified 3 pathogenic mutations in BRCA2 and calculated a 6% carrier frequency of BRCA2 mutations (95% CI: 2.1 - 12) [19]. In a retrospective study of 97 men with breast carcinoma, Tai et al. estimated a 6.8% cumulative risk of MBC for BRCA2 mutation carriers at 70 years of age (95% CI: 3.2 - 12) [22]. Risch et al. observed an increased MBC relative risk of 102 for BRCA2 mutation carriers versus non-carriers (95% CI: 9.9 - 1.050) [23]. Syrjakoski et al. screened a cohort of 154 MBC patients for BRCA2 mutations, and identified previously described founder or novel mutations in 12 (7.8%) cases [18]. Additionally, the authors found that 44% of patients with a positive family history of breast cancer carried a BRCA2 mutation, as compared to the 3.6% of patients without a family history (p < 0.0001) [18]. However, this positive association between family history and BRCA mutation carrier status has not been reproduced in other analysis. While Haraldsson et al. identified BRCA2 germ-line mutations in 7 (20.6%) of 34 cases and estimated a case mutation frequency of 16%, 86% of MBC cases carrying BRCA2 mutations had no family history of breast cancer [6]. Similarly, Ding et al. identified pathogenic BRCA2 mutations in 18 of 115 MBC cases, resulting in a BRCA2-mutation prevalence of 16% (95% CI: 11 - 24), though the difference in BRCA2-mutation frequencies between cases with and without family history of breast cancer was not statistically significant (p = 0.145), further indicating that family history is a weak predictor of mutation carrier status in males [15]. Moreover, Ottini et al. [26] reported that 50% of BRCA2 pathogenic mutations were in

<table>
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<tr>
<th>Study, year</th>
<th>Patients (N)</th>
<th>Outcomes</th>
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<tbody>
<tr>
<td>D’Avanzo, 1995</td>
<td>103</td>
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<td>Haraldsson, 1998</td>
<td>34</td>
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<td>Ewertz, 2001</td>
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<td>Johnson, 2002</td>
<td>1986</td>
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<td>Brinton, 2008</td>
<td>324,920</td>
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Abbreviations: OR = odds ratio, CI = confidence interval, MBC = male breast cancer, AR = androgen receptor gene, BRCA = breast cancer gene, RR = relative risk.
Table 2. Summary of all published studies evaluating genetic mutations as a risk factor for MBC* (1996-2011).

<table>
<thead>
<tr>
<th>Study, year</th>
<th>Patients (N)</th>
<th>Outcomes</th>
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| Couch, 1996 [4] | 50 | -Study design: germline DNA from 50 MBC cases (unselected for family history) analyzed for mutations in BRCA2  
-9 disease-associated mutations detected, with 7 of 9 seen in the 50 MBC cases  
-BRCA2 mutations estimated to account for 14% of MBC, all but one of which had a family history of male and/or female breast cancer |
| Thorlacius, 1996 [2] | 9 | -Study design: 9 families with a history of MBC studied to determine linkage between BRCA2 and hereditary MBC  
-Among mutation carriers, there are 12 MBC cases, accounting for 40% of all males diagnosed with breast cancer in Iceland over the past 40 years  
-3 (25%) of the 12 cases had no family history of breast cancer (no statistical significance reported) |
| Friedman, 1997 [3] | 54 | -Study design: population-based series of 54 MBC cases analyzed for germline mutations in BRCA1/2  
-No germline BRCA1 mutations found  
-2 (4%) MBC cases carried truncating BRCA2 mutations, and only 1 of those carrying a mutation had a family history of cancer (ovarian cancer in a first-degree relative) |
| Mavraki, 1997 [11] | 26 | -Study design: screening of DNA from 26 MBC cases to determine the frequency of BRCA2 germline mutations  
-BRCA2 mutation detected in 3 (12%) out of 26 cases  
-3 mutations resulting in frameshifts and premature termination of translation identified |
| Haraldsson, 1998 [1] | 34 | -Study design: the coding region of the BRCA2 and AR genes in breast tumors from 34 MBC patients were analyzed  
-No cases of germline AR mutations were observed, but the number of AR polyglutamine repeats were lower among BRCA mutation carriers  
-5 different BRCA2 germline mutations were seen in 7 (20.6%) of the 34 cases, all of which resulted in the formation of truncated protein products |
| Csokay, 1999 [9] | 18 | -Study design: case-control study of 64 cases and 81 controls to investigate whether increased length of CAG repeat sequence in AR is associated with development of MBC  
-There was no statistical significance in the distribution of CAG repeats in AR among MBC cases and controls ($p = 0.916$)  
-No difference between median CAG repeat length of cases and controls ($p = 0.765$)  
-Sequences of $\geq$ 30 repeats were found only among cases |
| Young, 2000 [5] | 145 | -Study design: population-based study of 94 MBC aimed to establish to prevalence of BRCA1 and BRCA2 mutations  
-No disease-associated mutations were identified in BRCA1  
-5 disease-associated variants were seen in BRCA2  
-The carrier frequency of BRCA2 mutations was 6% (95% CI: 2 - 13) |
| Basham, 2002 [22] | 94 | -Study design: prevalence of germline mutations in BRCA1/2 analyzed in 76 MBC cases  
-Deleterious mutations were seen in 21 (28%) of 76 cases, with 8 mutations occurring in BRCA1 and 14 in BRCA2(one Ashkenazi individual had one mutation in each gene) |
| Frank, 2002 [33] | 76 | -No statistical significance in mutation prevalence in men with a family history of breast or ovarian cancer versus those without  
-No statistical significance in mutation prevalence in MBC patients of Ashkenazi ancestry compared with those of non-Ashkenazi ancestry |
| Meijers-Heijboer, 2002 [29] | 2691 | -Study design: genome-wide linkage search of 718 families in which breast cancer susceptibility is not due to BRCA mutation  
-CHEK2*1100delC variant in 13.5% of patients from families with MBC ($p = 0.00015$)  
-CHEK2*1100delC variant results in an ~10-fold increase of MBC risk in non-carriers of BRCA1 and BRCA2 mutations (statistical significance not reported)  
-9% of MBC cases attributable to CHEK2*1100delC (statistical significance not reported) |
MBC cases without a family history of breast cancer, and Csokay et al. [16] found that 0 of 6 MBC cases with pathogenic BRCA2 mutations had a family history of breast cancer. In an analysis of 76 men with breast cancer, Frank et al. identified deleterious mutations in 28% of the cases, of which more than one-third occurred in BRCA1 [24]. These mutations were more prevalent in men with a family history of breast or ovarian cancer and in men of Ashkenazi ancestry, although these findings failed to achieve statistical significance (p = 0.1121 and p = 0.1117, respectively) [24]. In an analysis of 261 Israeli men with a diagnosis of breast cancer, Chodick et al. observed no difference in the BRCA1 or BRCA2 mutation carrier frequencies between Ashkenazi and non-Ashkenazi Jews, implicating that the increased incidence of MBC observed in Ashkenazi men cannot be accounted for by the prevalence of BRCA1/2 mutations alone [21]. Failure of BRCA mutation prevalence to reach statistical significance in men of Ashkenazi heritage is in stark contrast to the prevalence observed in their female counterpart. The prevalence of BRCA1 and BRCA2 mutations among Caucasian non-Ashkenazi Jewish women with breast cancer is 2.2% - 2.9% and 2.2%, respectively, and 8.3% - 10.2% and 1.1%, respectively, among Ashkenazi Jewish women with breast cancer [25] [27]. While the prevalence of BRCA1 and BRCA2 mutations among African American women with breast cancer is noted to be 1.3% - 1.4% and 2.6%, respectively [25] [27], the prevalence among the male African American population has yet to be specifically analyzed. However, the incidence of breast cancer is higher among black men of all ages (1.8 per 100,000) when compared to their age-related white counterparts (1.1 per 100,000), and afflicted black males display poorer prognostic features, including advanced-stage disease, with more extensive nodal involvement, larger tumor sizes, and higher tumor grade [2]. While racial disparities in outcomes in women with breast cancer are well studied, those in men warrant further investigation.
4.2. Other Genes Associated with MBC

Various additional genetic mutations have been implicated in the development of male breast cancer, however these mutations account for far less cases than the previously discussed BRCA1/2 mutations. The PALB2 gene product plays a role in the localization and stabilization of BRCA2 in nuclear chromatin, which is essential for BRCA2 to function in DNA repair. Ding et al. postulated that PALB2 may confer risk to develop MBC as a result of its close relationship to BRCA2 [15]. The authors screened for mutations in the PALB2 gene in BRCA2-negative MBC cases and identified 14 germ-line variants, which accounted for 1% - 2% of male breast cancers [15]. The CYP17 gene codes for an enzyme involved in the synthesis of androgens and estrogens. A known single base pair polymorphism creates an additional promotor motif, which has been hypothesized to lead to increased transcriptional activity and enhanced steroid hormone production. That said, Gudmundsdottir et al. investigated the association between CYP17 polymorphism and male breast cancer risk and found no difference in genotype frequencies between MBC cases and controls [14].

The consistently elevated risk of MBC reported in the MVI may suggest the presence of mammary carcinogens in gasoline vapors, and further investigation is warranted.

5. Occupational Exposures

Five studies involving a total of 16,667 patients (Table 3) have addressed occupational exposure as a risk factor from MBC. McLaughlin et al. assessed the incidence of male breast cancer by occupational and industrial categories to elucidate environmental and occupational risk factors [28]. Those industries and occupations with a significantly (p < 0.05) increased incidence of male breast cancer were determined from a sample of 333 cases of male breast cancer [28]. The highest risk (~8-fold) was observed in men employed in making soap and perfume, which the authors attributed to the production of estrogen-containing cosmetic creams by this population [26]. A meta-analysis of 7 case-control and 11 cohort studies by Sun et al. revealed a statistically significant increased risk of MBC with electromagnetic field exposure as well (pooled ORs = 1.32, 95% CI = 1.14 - 1.52, p < 0.001), and subgroup analyses also showed similar results [29]. Cocco et al. conducted a case-control of 178 MBC cases and 1041 controls to investigate whether risk of MBC is associated with workplace exposures [30]. A significant risk in MBC was associated with employment in blast furnaces, steel works, rolling mills (OR = 3.4, 95% CI: 1.1 - 10.1), and motor vehicle manufacturing (OR = 3.1, 95% CI: 1.2 - 8.2), however the authors did not hypothesize a cause for this association [30]. A case-control study of 104 MBC cases and 1901 controls by Villeneuve et al. failed to confirm the elevated risk of MBC in blast furnaces, steel works, and rolling mills [31]. However, these authors noted a two-fold increase in MBC incidence among motor vehicle mechanics (95% CI: 1.0 - 4.4), with a dose-response relationship related to duration of employment (OR = 5.9 in motor vehicle mechanics employed for 10 or more years, 95% CI: 2.4 - 14.6) [31]. Furthermore, a significantly increased odds ratio of 1.8 was observed in those cases employed in the motor vehicle sales and repairs industry (95% CI: 1.6 - 3.2) [31]. Similarly, Hansen reported a MBC odds ratio of 2.5 for males employed in trades with potential exposure to gasoline and combustion products for a period of more than 3 months (95% CI: 1.3 - 4.5), and an odds ratio of 5.4 among men younger than 40 years of age at the time of first employment (95% CI: 2.4 - 11.9) [32]. The consistently elevated risk of MBC reported in the MVI may suggest the presence of mammary carcinogens in gasoline vapors, and further investigation is warranted.

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<th>Study, year</th>
<th>Patients (N)</th>
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- The highest occupational risk (SIR = 7.6) was seen in men employed in the soap- and perfume-making industry (p < 0.01) |
| Cocco, 1998 [21]  | 1219         | -Study design: case-control study of 178 cases of MBC and 1041 controls to investigate risk of MBC with workplace exposures. 
- Increase in MBC risk associated with employment in blast furnaces, steel works, and rolling mills (OR = 3.4, 95% CI: 1.1 - 10.1) 
- Increase in MBC risk associated with employment in the MVI (OR = 3.1, 95% CI: 1.2 - 8.2) |
| Hansen, 2000 [28] | 13,110       | -Study design: case-control study of 230 cases and 12,880 controls on the association between MBC morbidity and occupational exposure. 
- OR = 2.5 (95% CI: 1.3 - 4.5) for men with >3 months of employment in occupations with potential exposure to gasoline and combustion products. 
- OR = 5.4 for men employed at <40 years of age (95% CI: 2.4 - 11.9) |
| Villeneuve, 2010 [27] | 2005         | -Increased MBC risk in motor vehicle mechanics (OR = 2.1, 95% CI: 1.0 - 4.4), with increased risk if employed ≥10 years (OR = 5.9, 95% CI: 2.4 - 14.6) 
- Increased risk in sale/repair of motor vehicles (OR = 1.8, 95% CI: 1.0 - 3.2) |
| Sun, 2013 [34]    | Meta-analysis | -Study design: a meta-analysis of 7 case-control and 11 cohort studies to confirm a possible association between MBC and EMF exposure. 
- Increased risk of MBC with EMF exposure was defined (pooled ORs = 1.32, 95% CI: 1.14 - 1.52, p < 0.001 |

Abbreviations: MBC = male breast cancer, SIR = standardized incidence ratio, EMF = electromagnetic field, MVI = motor vehicle industry, OR = odds ratio, CI = confidence interval. *p value: statistical significance, <0.05.

6. Abnormalities in the Androgen-to-Estrogen Ratio

Eleven studies including a total of 4,843,598 patients (Table 4) assessed the risk of MBC in the setting of abnormal androgen-to-estrogen ratios. Nirmul et al. examined the endocrine profiles of 8 MBC patients compared to 8 healthy matched controls [33]. These authors found that the mean total serum estradiol level and the calculated mean free estradiol index were significantly increased in MBC cases compared to controls (p < 0.01 and p < 0.01, respectively) [33]. The two groups showed no significant differences in the levels of luteinizing hormone, follicle stimulating hormone, prolactin, dehydroepiandrosterone-sulfate, testosterone, or sex-hormone binding globulin [33]. Brinton et al. conducted an analysis within the U.S. Veterans Affairs (VA) medical care system database involving a total of 4,501,578 patients, from which they identified 642 MBC cases [34]. Medical conditions significantly associated with increased MBC risk in decreasing order were Klinefelter’s syndrome (RR = 29.64, 95% CI: 12.26 - 71.68), gynecomastia (RR = 5.86, 95% CI: 3.74 - 9.17), obesity (RR = 1.98, 95% CI: 1.55 - 2.54), orchitis/epididymitis (RR = 1.84, 95% CI: 1.10 - 3.08), and diabetes (RR = 1.30, 95% CI: 1.05 - 1.60) [34]. After adjusting for obesity, the association with diabetes disappeared, but that with gynecomastia persisted [34]. Notably, additional studies by Casagrande et al. [35] (N = 150) and Hsing et al. [36] (N = 690) have negated the significance of the association between gynecomastia and MBC, and Olsson et al. [37] observed no new cases of MBC in a cohort of 446 men with a diagnosis of gynecomastia after a maximum follow-up time of 30 years. The association between increased MBC risk and obesity has been further supported by Brinton et al. in their prospective analysis of 324,920 men, including a total of 121 MBC cases (RR = 1.79, 95% CI: 1.10 - 2.91, for body mass indices, BMI, of ≥30 versus <25 kg/m²) [7]. These authors additionally noted that physical activity during adolescence was inversely associated with MBC risk (for activity ≥5 times per week, RR = 0.59, 95% CI: 0.31 - 1.13), and that subjects who had a physically active routine were at a statistically significant lower risk of MBC (RR = 0.49, 95% CI: 0.28 - 0.87) [7]. Casagrande et al. similarly observed a significant increase in relative risk of breast cancer with increasing weight recorded at age 30 in their case-control study of 75 MBC patients [35]. Men who weighed 90 or more kilograms at age 30 years had more than 5 times
Table 4. Summary of all published studies evaluating androgen-to-estrogen ratio abnormalities as a risk factor for MBC* (1982-2010).  

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<th>Study, year</th>
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<th>Outcomes</th>
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| Nirmul, 1982 [14] | 16 | - Study design: case-control of 8 MBC cases of ductal carcinoma and 8 controls to analyze the sex-hormone profile of MBC patients  
- No significant difference in the mean fasting levels and ranges of LH, FSH, PRL, DHEA-S, and SHBG in the cases when compared to the controls  
- Mean total serum estradiol-17β level and calculated mean free estradiol index increased in cases (p < 0.02) |
| Casagrande, 1988 [18] | 150 | - Study design: case-control of 75 cases and 75 controls to investigate suspected risk factors  
- Men who weighed ≥90 kg at age 30 had >5x the breast cancer risk of men weighing <60 kg at that age (RR = 5.45 and RR = 1.00, respectively, p = 0.04)  
- No significant difference observed between cases and controls with respect to frequency of alcohol consumption  
- Gynecomastia was not found to be a significant risk factor |
| Hsing, 1998 [19] | 690 | - Increased risk for men described as having been very overweight (OR = 2.3, 95% CI: 1.1 - 5.0)  
- Dose-response relationship seen between risk and BMI (p < 0.01)  
- No association found for alcohol use |
| Sorensen, 1998 [20] | 11,642 | - Study design: males with a diagnosis of liver cirrhosis followed for a mean of 4.3 years to assess risk of breast cancer and men with cirrhosis  
- 3 cases observed (SIR = 4.0, 95% CI: 0.8 - 11.7) |
| Ewertz, 2001 [23] | 624 | - Study design: population-based case-control study of 156 cases and 468 controls  
- Increased risk of MBC associated with obesity 10 years before diagnosis (OR = 2.1; 95% CI: 1.0 - 4.5), and diabetes (OR = 2.6, 95% CI: 1.3 - 5.3) |
| Altinli, 2002 [24] | 40 | - Average BMI = 26.54 kg/m² (above the World Health Organization upper limit of normal)  
- 23 (57.5%) out of 40 patients were above their ideal body weight (statistical evaluation not performed due to small sample size) |
| Johnson, 2002 [25] | 1986 | - Study design: analysis of risk factors in a population-based case-control study of 81 newly diagnosed, histologically confirmed MBC cases and 1905 male controls  
- Increased risk of MBC in overweight cases (OR = 2.19, 95% CI: 1.08 - 4.43) |
| Olsson, 2002 [26] | 446 | - Study design: prospective cohort study of men with histological diagnosis of gynecomastia  
- No new cases of MBC seen at the end of median follow-up time (266 months) |
| Guenel, 2004 [13] | 1506 | - Risk of MBC increased by 16% (95% CI: 7 - 26) per 10 grams of alcohol per day (p < 0.001)  
- OR = 5.89 (95% CI: 2.21 - 15.69) for alcohol intake >90 grams/day |
| Brinton, 2008 [16] | 324,920 | - Study design: prospective NIH-AARP Diet and Health Study, of 121 MBC patients  
- Obesity was positively related to risk (RR = 1.79, 95% CI: 1.10 - 2.91, for BMI >30 vs< 5 kg/m²) and physical activity inversely related, even after adjustment for BMI |
| Brinton, 2010 [15] | 4,501,578 | - Study design: MBC etiologic factors assessed from 642 cases of primary MBC documented in the U.S. Veterans Affairs medical care database  
- Medical conditions related to MBC risk: diabetes (RR = 1.30, 95% CI: 1.05 - 1.60), obesity (1.98, 1.55 - 2.54), orchitis/epididymitis (1.84, 1.10 - 3.08), Klinefelter’s syndrome (29.4, 12.26 - 71.68), gynecomastia (5.86, 3.74 - 9.17)  
- Cholelithiasis an MBC risk for black patients (RR = 3.45, 95% CI: 1.59 - 7.47)  
- After adjusting for obesity, the association between MBC and diabetes disappeared, but that between MBC and gynecomastia persisted |

Abbreviations: MBC = male breast cancer, BMI = body mass index, NIH = national institutes of health, RR = relative risk, CI = confidence interval, OR = odds ratio, LH = luteinizing hormone, FSH = follicle stimulating hormone, PRL = prolactin, DHEA-S = dehydroepiandrosterone sulfate, SHBG = sex hormone-binding globulin, SIR = standardized incidence ratio.  
*p value: statistical significance, <0.05.

The risk of breast cancer than men weighing less than 60 kilograms at that age (RR = 5.45 and RR = 1.00, respectively, p = 0.04) [35]. In a case-control study of 178 men who died of breast cancer, Hsing et al. reported an increased risk of MBC for men who were described by their next-of-kin as very overweight (OR = 2.3, 95% CI: 1.1 - 5.0) [36]. Similarly, Ewertz et al. [10] (N = 624) reported an increased risk of MBC in males whose BMI...
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Excessive alcohol has also been postulated to increase MBC risk as a result of its influence on hormone levels. Guenel et al. investigated the role of alcohol consumption in 74 MBC patients and 1432 age-matched controls [39]. In comparison to age- and geographically-matched controls, the risk of developing breast cancer in men increased by 16% (95% CI: 7 - 26) per 10 grams of alcohol per day (p < 0.001) [39]. Additionally, an odds ratio of 5.89 (95% CI: 2.21 - 15.69) was observed for alcohol intake greater than 90 grams per day as compared with light consumption of less than 15 grams per day, and the authors concluded that the relative risk of male breast cancer increases with consumption levels [39]. Conversely, despite a large sample size (N = 4,501,578) of VA patients with an admission diagnosis of alcoholism, Brinton et al. found no evidence of alteration in MBC risk in subgroup analysis, and further failed to detect an association of MBC with liver cirrhosis secondary to either alcohol consumption or other causes [34]. Similarly, Brinton et al. [7] and Casagrande et al. [35] found no evidence for a relationship between excessive alcohol consumption and increased MBC risk, and separate analyses by Ewertz et al. [10] and Sorensen et al. [40] (N = 11,642) involving men with liver cirrhosis also failed to detect a significant increase in MBC risk.

7. Conclusions

Male breast cancer is an uncommon disease entity which typically presents with poor prognostic features, advanced stage, large tumor size, frequent lymphatic invasion, and early chest wall spread [3]. Large-scale epidemiologic studies have been difficult to conduct as a result of the disease’s rarity. However, current published literature indicates that MBC is similar to its female counterpart clinically, in that various familial, genetic, hormonal, and environmental factors predispose at-risk populations to its development.

Public and physician awareness about male populations at risk for breast cancer is limited, if not non-existent, and men diagnosed with breast cancer are likely to suffer from psychological concerns including stigma, altered body image, lack of emotional support and feelings of isolation, and disease misperceptions [41]-[44]. As a result of poor knowledge about MBC among the public and healthcare community, there are currently no guidelines for breast cancer screening in male populations, even among those at high risk for the disease, which leads to delays in diagnosis and management. This fact, combined with data suggesting that males present with advanced stage disease, clearly implies the need for more defined screening criteria in select subgroups.

Individuals who fulfill one or more high risk criterion should be provided routine surveillance via clinical examination and imaging. Fifty to ninety percent of MBC cases present initially with a palpable breast mass [45]-[47]. This finding dictates a role for physical examination of the breast in high-risk male populations. Current National Comprehensive Cancer Network (NCCN) guidelines for men with BRCA1/2 mutations recommend that healthcare providers teach and encourage breast self-examination and perform clinical breast examinations twice a year [2]. We recommend that those guidelines be broadened to include the following five high-risk populations: 1) males with a previous personal history of breast carcinoma, 2) males with a strong family history of breast cancer (defined as an affected mother or sister), 3) confirmed BRCA2 mutation carriers (regardless of family history), 4) males with a diagnosis of Klinefelter’s syndrome, and 5) males employed in the chemical manufacturing or motor vehicle industry. Mammography should serve as an additional means of screening for the aforementioned populations. Mammographic screening has proven to be greater than 90% sensitive and specific in diagnosing malignant lesions in the male breast, with a negative predictive value of 99% for all categories of benign disease [48]. In light of this data, the five high-risk populations outlined above may benefit from annual clinical mammography in addition to bi-annual clinical examination. Lastly, there exist important management implications for BRCA2 carriers. Genetic testing for BRCA2 should be recommended for any MBC patient, regardless of family history of breast cancer, due to the large percentage of BRCA2 pathogenic mutations recorded in MBC patients lacking a family history of breast cancer.

In conclusion, select male high risk populations may benefit from routine breast cancer surveillance with bi-annual physician physical examination and yearly mammography. Public awareness of male breast cancer, particularly to those at high risk of MBC, is substantially lacking and serves as an obstacle to effective screening. Increased public and physician education on male breast cancer and the development of preventative health
campaigns for at-risk populations should help to raise awareness about the rare disease and the need for screening of at-risk populations [47] [49]-[54].

**Author Disclosure Statement**

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