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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 gremline 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].

Table 1. Summary of all published studies evaluating family history as a risk factor for MBC* (1995-2008).

Study, year	Patients (N)	Outcomes
D'Avanzo, 1995 [17]	103	-Study design: a case-control study of 21 MBC cases and 82 controls admitted to the hospital for acute, non-neoplastic, non-hormone related disease -A history of BC in female relatives resulted in an MBC OR of 8.5 (95% CI: 1.1 - 69.0)
Haraldsson, 1998 [1]	34	-Study design: analysis of germline mutations in 34 MBC patients -1 (14%) out of 7 BRCA2 mutation carriers had a positive family history of BC -13% of cases overall had a positive family history of BC
Ewertz, 2001 [23]	624	-Study design: population-based case-control study of 156 cases and 468 controls -Increased risk of MBC associated with BC family history (OR = 3.3; 95% CI: 2.0 - 5.6)
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 breast cancer risk seen in men with a mother or sister with BC (adjusted OR = 3.65, 95% CI: 1.62 - 8.19)
Brinton, 2008 [16]	324,920	-Study design: prospective National Institutes of Health-AARP Diet and Health Study, of 324,920 men, among whom 121 developed breast cancer. -Men with a first-degree relative with BC had an increased risk of breast cancer (RR = 1.92, 95% CI: 1.19 - 3.09)

Abbreviations: OR = odds ratio, CI = confidence interval, MBC = male breast cancer, AR = androgen receptor gene, BRCA = breast cancer gene, RR = relative risk.

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 promotor 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 5 pathogenic mutations in BRCA2 and calculated a 6% carrier frequency of BRCA2 mutations (95% CI: 2 - 13) [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 2. Summary of all published studies evaluating genetic mutations as a risk factor for MBC* (1996-2011).

Study, year	Patients (N)	Outcomes
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: a series of 18 MBC patients analyzed for germ-line mutations in BRCA1/2 -No germline BRCA1mutation was observed -6 (33%) of the 18 MBC cases carried truncating mutations in the BRCA2gene and none of them reported a family history for breast/ ovarian cancer -4 (22%) patients had a family history of breast/ovarian cancer in ≥1 first- or second-degree relative; no BRCA2mutation was detected among them
Young, 2000 [5]	145	-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 ≥30 repeats were found only among cases
Basham, 2002 [22]	94	-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)
Frank, 2002 [33]	76	-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) -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)

Continued

Gudmundsdottir, 2003 [7]	348	-Study design: case-control study of 39 MBC cases and 309 controls to investigate the association between the CYP17 polymorphism and MBC risk -No significant difference seen in the CYP17 genotype frequencies of cases and controls
Syrjakoski, 2004 [12]	154	-Study design: cohort study of 154 MBC cases analyzed to determine frequency of BRCA2 founder mutations -Founder mutations detected in 10 (6.5%) patients -2 novel mutations detected in the BRCA2 coding region of 34 (22%) out of 154 samples -3 MBC patients had a first- or second-degree relative with ovarian cancer, and 2 of these MBC patients carried BRCA2 mutations (statistical significance not reported) -44% of patients with a family history of breast and/or ovarian cancer were BRCA2 mutation carriers, versus 3.6% of those with no family history ($p < 0.0001$)
Risch, 2006 [32]	1171	-Study design: population series of 1171 patients with ovarian cancer were screened for the presence of BRCA1/2 mutations with respect to cancers reported among their relatives -Higher MBC risk associated with BRCA2 mutation carriage than with noncarriage, (RR = 102, 95% CI = 9.9 - 1.050)
Tai, 2007 [31]	97	-Study design: retrospective study analyzing the MBC risk for BRCA1/2 mutation carriers -Estimated cumulative risk of MBC for BRCA1 mutation carriers at age 70 years is 1.2% (95% CI: 0.22 - 2.8), and for BRCA2 mutation carriers is 6.8% (95% CI: 3.2 - 12)
Chodick, 2008 [30]	261	-Study design: Israeli men diagnosed with breast cancer screened to evaluated the contribution of BRCA mutations to MBC -A total of 29 BRCA1 and BRCA2 mutations detected -BRCA1 and BRCA2 mutation carrier frequencies were not statistically different between Ashkenazi (12.8%) and non-Ashkenazi Jews (9.1%)
Ottini, 2009 [10]	108	-Study design: population-based study of 108 MBC cases -2 (1.9%) cases carried BRCA1 mutations, and 8 (7.4%) cases carried BRCA2 mutations -Significant association between BRCA2-related tumors and high tumor grade ($p = 0.005$)
Ding, 2011 [8]	115	-Study design: genome sequencing performed on 115 MBC cases to determine the frequency of pathogenic mutations in BRCA2 and PALB2 -Pathogenic BRCA2 mutations seen in 18 of the 115 MBC cases, resulting in a BRCA2 mutation prevalence of 16% (95% CI: 11 - 24) -The difference in BRCA2-mutation frequencies between cases with and without family history of breast cancer was not statistically significant ($p = 0.145$) -Of the BRCA2-negative cases, 1% - 2% exhibited a pathogenic PALB2 mutation (statistical significance not reported)

Abbreviations: MBC = male breast cancer, AR = androgen receptor gene, BRCA = breast cancer gene, CI = confidence interval, PALB2 = partner and localizer of BRCA2 gene. *p value: statistical significance, <0.05.

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 BRCA1andBRCA2 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 CHEK2 gene located on chromosome 22 encodes a cell-cycle checkpoint kinase that is implicated in DNA repair processes involving BRCA1 and p53. Meijers-Heijboer *et al.* showed that a known truncating variant of the gene has a frequency of 1.1% in healthy individuals, but is present in 13.5% of individuals from families with male breast cancer ($p = 0.00015$) [20]. The authors estimated that this CHEK2 variant confers an ~10-fold increase in the risk of MBC that may account for ~9% of male breast cancers [20]. Haraldsson *et al.* surmised that mutant Androgen Receptor (AR) genes may exhibit an altered sequence-specific DNA binding, possibly having acquired the ability to bind to estrogen-responsive elements and to activate estrogen-regulated genes, though they found no evidence of germ-line or somatic AR mutations among 34 MBC cases [6]. A region within exon 1 of the gene coding for the AR is highly polymorphic and contains a variable number of CAG repeats, with *in vitro* studies revealing that a short CAG repeat sequence increases the level of transactivation of the androgen receptor [13]. Young *et al.* investigated whether increased length of the CAG repeat sequence in the AR gene is associated with the development of MBC [13]. While the authors did not observe a significant overall difference between the median number of CAG repeat length of MBC cases and controls, sequences of 30 or more repeats were only observed in MBC cases, leading the authors to surmise that a relatively long CAG repeat sequence within the AR gene may be implicated in MBC, and a short sequence may offer protection against MBC [13].

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: 1.0 - 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.

Table 3. Summary of all published studies evaluating occupational exposure as a risk factor for MBC* (1988-2013).

Study, year	Patients (N)	Outcomes
McLaughlin, 1988 [6]	333	-Study design: systematic review of 333 MBC cases to assess the incidence by occupational and industrial categories -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	-Study design: investigation of MBC occupational risk factors in a case-control study of 104 cases and 1901 controls -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/m^2) [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).

Study, year	Patients (N)	Outcomes
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	-Study design: case-control study of 178 MBC mortalities and 512 male controls who died of other causes to investigate risk factors -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	-Study design: retrospective review of all MBC patients who underwent surgery to examine relation between BMI and MBC -Average BMI = 26.54 kg/m^2 (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	-Study design: case-control study of 74 histologically verified MBC cases and 1432 age-matched controls to investigate the role of alcohol drinking in MBC -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/m^2) 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 hormor, 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

exceeded 30 ten years prior to diagnosis (OR = 2.1, 95% CI: 1.0 - 4.5), and Altinli *et al.* [38] observed an average BMI of 26.54 in 40 MBC patients, with 23 (57.5%) of these patients being above their ideal weight as defined by the World Health Organization (statistical analysis not performed due to limited sample size). Johnson *et al.* (N = 1986) also reported a higher risk of MBC in overweight cases (OR = 2.19, 95% CI: 1.08 - 4.43) [8].

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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