Review

Epidemiology of Male Breast Cancer

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Abstract

Breast cancer in men is a rare disease, accounting for ~1% of all breast cancer cases. Although the epidemiologic literature regarding female breast cancer is extensive, relatively little is known about the etiology of male breast cancer (MBC). This review is intended to summarize the existing body of evidence on genetic and epidemiologic risk factors for breast cancer in men. Overall, the epidemiology of MBC presents similarities with the epidemiology of female breast cancer. Major genetic factors associated with an increased risk of breast cancer for men include *BRCA2* mutations, which are believed to account for the majority of inherited breast cancer in men, Klinefelter syndrome, and a positive family history. Suspected genetic factors include *AR* gene mutations, *CYP17* polymorphism, Cowden syndrome, and *CHEK2*. Epidemiologic risk factors for MBC include disorders relating to hormonal imbalances, such as obesity, testicular disorders (e.g., cryptorchidism, mumps orchitis, and orchiectomy), and radiation exposure. Suspected epidemiologic risk factors include prostate cancer, prostate cancer treatment, gynecomastia, occupational exposures (e.g., electromagnetic fields, polycyclic aromatic hydrocarbons, and high temperatures), dietary factors (e.g., meat intake and fruit and vegetable consumption), and alcohol intake. (Cancer Epidemiol Biomarkers Prev 2005;14(1): 20–6)

Introduction

Breast cancer in men is a rare disease, accounting for <1% of all breast cancer cases in the United States (1) and ~0.1% of cancer mortality in men (2-5). The American Cancer Society estimates that 1,450 men will be diagnosed with breast cancer in the United States and 470 will die from this disease in the year 2004 (6). The incidence of male breast cancer (MBC), once thought to be relatively stable, now seems to be substantially increasing (7). Incidence of MBC increased significantly from 0.86 to 1.06 per 100,000 population over the last 26 years (7). The worldwide variation of MBC resembles that of breast cancer in women, with higher rates in North America and Europe and lower rates in Asia (2, 8). Although the epidemiologic literature on female breast cancer (FBC) is extensive, little is known about the etiology of MBC. This difference is mostly due to the rarity of this disease in men, which greatly limits the application of epidemiologic methodology to studies of MBC. Due to the rarity of the cancer, sample size is often too small to observe an association between the risk factor and breast cancer. Tissue availability presents another challenge. Most breast tumors in men are small, leaving little tissue for research purposes after the requisite pathology workup for molecular and genetic studies. This review is intended to summarize the existing body of evidence on genetic and epidemiologic risk factors for breast cancer in men.

Genetic Factors

Family History. Similar to FBC, a positive family history of breast cancer is associated with increased risk of MBC. A population-based series of 54 MBC cases (9) observed that 17% of MBC patients have at least one first-degree relative with breast cancer. This is similar to a study by Hill et al. (10), which observed that 19 of 123 (15%) patients had a first-degree relative with a history of breast cancer and noted that a family history was not associated with mean age at onset for the men nor was it associated with survival. Two other population-based studies also observed that ~20% of male cases had a history of breast cancer in a female relative (11, 12). A limited number of studies (8, 10-14) examined the effect of a positive family history of MBC on risk. However, results from these studies are difficult to interpret due to the rarity of such events, which can greatly influence risk estimates. For instance, Casagrande et al. (13) reported such history among only one MBC patient leading to an odds ratio of infinity. Investigations of the effect of a family history of FBC have produced more stable results (8, 11, 13-15). In general, results from these investigations suggest that a positive family history of either male or female breast carcinoma among first-degree relatives was associated with a 2- to 3-fold increase in MBC risk.

In women, between 30% and 86% of inherited breast cancer are estimated to be etiologically linked to germ line mutations in highly penetrant susceptibility genes, such as *BRCA1* and *BRCA2* (16-18). In contrast, estimates have ranged from 4% to 40% for the proportion of MBC that has been attributed to inherited mutations (9, 19-21). Genes that have been implicated in the etiology of MBC include *BRCA2*, *AR* gene, cytochrome P45017 (*CYP17*), the XXY karyotype (Klinefelter syndrome), the *PTEN* tumor suppressor gene associated with Cowden syndrome, and the *CHEK2* gene.

BRCA2. The *BRCA2* gene is located on chromosome 13q12-13 (22) and has been associated with the majority of inherited breast cancer in men. *BRCA2* has recently been noted to regulate the intracellular localization and DNA-binding ability of RAD51, and loss of these abilities following inactivation of *BRCA2* may be an important event leading to genomic instability and tumorigenesis (23). *BRCA1* mutations are estimated to exist in <5% of all FBCs (24). Similarly, *BRCA1* mutations are rare in MBC. Most studies have observed no carriers of *BRCA1* mutations (9, 25-28); however, a few studies have observed *BRCA1* mutations in males with breast cancer. Ottini et al. (29) observed that 1 of 25 (4%) MBC cases from Florence, Italy, had a mutation in

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BRCA1. A study by Struewing et al. (30) observed that 4 of 110 (3.6%) Ashkenazi Jewish men carried a mutation in *BRCA1*, and a study by Frank et al. (31) found that 10.5% (8 of 76) of Ashkenazi Jewish men with breast cancer had mutations in *BRCA1*. Germ line *BRCA2* mutations, on the other hand, have been found in 10% to 20% of FBCs among women with a strong family history of breast cancer (32) and in 4% to 40% of MBCs, suggesting considerable variation across populations (9, 19-21). For example, Friedman et al. (9) analyzed a population-based series of 54 MBC cases in southern California and identified only 2 (4%) *BRCA2* mutation carriers. This is in contrast with a population-based Icelandic study (19) in which 40% of all males with breast cancer are carriers of the founder *BRCA2* mutation. Couch et al. (20) reported an intermediate mutation rate of 14% in a study of 50 MBC patients unselected for family history. In a Swedish population-based study, germ line truncating mutations were identified in 7 of 34 (21%) MBC cases (21), and a Hungarian hospital-based study (27) noted that 33% (6 of 18) of cases had a *BRCA2* mutation. These studies suggest that the frequency of *BRCA2* mutations might reflect broad genetic differences across populations. However, sample sizes of investigations to date have been very small, warranting caution in the interpretation of estimates.

A common mutation in the *BRCA2* gene is a 999del5 mutation. In a study of MBC patients in Iceland, the constitutional 999del5 mutation was shown to be involved in 40% of the cases (19). There is good evidence that a high proportion of inherited breast cancer in Iceland is due to this 999del5 founder mutation in the *BRCA2* gene, which has been traced back to a common ancestor in the beginning of the 16th century. This founder effect is similar to that in Ashkenazi Jewish women with a *BRCA1* mutation (18). In Ashkenazi Jewish women, there is a specific 6174delT mutation that occurs in the *BRCA2* gene (18). Ashkenazi Jewish women also have a high frequency of a 185delAG mutation in the *BRCA1* gene (18). These same mutations seem to be frequent in Ashkenazi Jewish men. Israeli investigators (30) examined MBC cases from five Israeli hospitals during 1980 to 1997 and noted that 19 of 110 cases carried mutations in the *BRCA1*/*BRCA2* genes. Fifteen of the 19 carriers exhibited a 6174delT mutation in the *BRCA2* gene, whereas the other four mutations were a 185delAG in the *BRCA1* gene.

Another *BRCA2* mutation noted to be associated with MBC is the duplication of 9p23-24, described in a family in which the father and all three sons had breast cancer (34). Genetic screening of all three sons revealed two constitutional *BRCA2* abnormalities: (*a*) an insertion A at nucleotide 2,041 in exon 10, which can lead to premature termination of the encoded protein at codon 615, and (*b*) a tandem interstitial duplication involving chromosome bands 9p23-24 (34). It is very likely that the *BRCA2* mutations contributed to breast cancer in this family, as familial clusters of four MBC cases are extremely rare, and the abnormality on 9p was present in all three sons (34).

Few studies have examined the cumulative risk of breast cancer in male carriers of the *BRCA2* gene. Easton et al. (35) studied two large linked families to estimate the age-specific risks of breast cancer in *BRCA2* mutation carriers. The authors estimate the cumulative risk for MBC by age 70 to be 6.3% (95% confidence interval, 1.4-25.6) or a relative risk ~150-fold the general population rates. More recently, Thompson et al. (36) examined 164 families with breast/ovarian cancer and germ line *BRCA2* mutations and reported similar results. Included among these families were 59 cases of MBC. The authors estimate a cumulative risk of 6.92% by age 80 for male carriers of the *BRCA2* mutation.

From a familial perspective, many studies have not shown an expected association between a positive family history of breast cancer and *BRCA2* mutations. For example, in one study, the authors noted that among 40 males with a family history of breast cancer six *BRCA2* mutations were observed (20). Alternatively, Csokay et al. (27) observed that 6 of 18 Hungarian men in a hospital-based study had *BRCA2* mutations, but surprisingly no *BRCA2* mutation was identified among the cases with a family history of breast or ovarian cancer. The lack of observed mutations in MBC cases with a positive family history could be due to several reasons: (*a*) methods used for mutation screening are not completely sensitive; thus, some aberrations, such as noncoding mutations, could have been missed (9); (*b*) a positive family history of breast cancer may include sporadic FBCs due to the high prevalence of such cancers in the general population (9); (*c*) there may be unknown inherited breast cancer susceptibility genes that confer a risk of MBC (9, 26, 37); and (*d*) because of small sample sizes, absence of a relationship between family history and *BRCA2* mutations could be due to chance.

Klinefelter Syndrome. Klinefelter syndrome has been consistently associated with breast cancer in men. The syndrome is characterized by a rare chromosomal abnormality of 47 XXY karyotype and occurs in ~1 in 1,000 men (38, 39). It is a hereditary disorder and not usually recognized until after puberty. Patients typically exhibit a eunuchoid habitus, gynecomastia, and small, firm testes and have increased secretion of follicle stimulating hormone (38-40). Men with Klinefelter syndrome also tend to have increased levels of gonadotropins but low levels of androsterone and normal to somewhat low levels of estrogens, resulting in a high estrogen/androgen ratio (39, 40). The mean age of breast cancer patients with Klinefelter syndrome is 58 years, which is somewhat lower than the mean age at onset of breast cancer in the absence of the syndrome (39). Three percent to 4% of MBC cases have been reported to have Klinefelter syndrome (38, 40). When compared with the frequency of the disorder in the general population, it seems that the breast cancer might be at least 20 times more common in males with Klinefelter syndrome compared with males without this condition (41, 42). Hultborn et al. (43) found that 7.5% of 93 male breast carcinoma cases from western Sweden were affected by Klinefelter syndrome. Based on their findings and on the prevalence of Klinefelter syndrome (43) in the normal population as well as the incidence of MBC, Hultborn et al. determined that there is a 49-fold increased risk of the development of breast cancer for men with Klinefelter syndrome. A possible explanation for increased risk in men with this disorder is abnormal hormonal stimulation of cell proliferation in mammary ductal epithelium (40, 41). A second theory proposes that increased risk of breast cancer may be due to treatment with exogenous testosterone, which is converted to estrogens in peripheral adipose tissue (40, 41, 44).

***AR* Gene Mutation.** Germ line mutations in the *AR* gene have also been suggested to predispose to MBC. Wooster et al. (45) first reported an association between development of breast cancer in two brothers and a germ line mutation in exon 3 encoding the DNA-binding domain of the *AR*. In a small study, Lobaccaro et al. (46) screened MBC patients and noted that 1 of the 13 patients had a point mutation in exon 3 encoding part of the DNA-binding domain. However, studies by Haraldsson et al. (21) and Syrjakoski et al. (47) found no evidence of germ line or somatic mutations in the *AR* gene. The *AR* gene has highly polymorphic polyglutamine (CAG) and polyglycine (GGC) tracts within the coding area of exon 1. Long CAG repeats have been implicated in FBC most likely by decreasing the capacity of the receptor to activate transcription (48). CAG repeats among MBC patients have been examined in three studies, and no statistically significant association between CAG repeat length and MBC were observed (9, 47, 49), although one study observed long repeats only among the MBC cases (49). Most of these studies are hampered by small sample sizes and are often limited to MBC patients who are still alive at the time of the study contributing to possible

selection bias. It has been proposed that the *AR* develops the ability to bind to estrogen response elements and therefore activate estrogen-regulated genes (46). Alternatively, the role of *AR* mutations in MBC may relate to the reduction in androgen levels, and subsequent elevated estrogen/androgen activity ratio may promote breast cancer development in men (21, 46, 50).

***CYP17* Gene.** Another gene hypothesized to be associated with male breast carcinoma is *CYP17*, which codes for the cytochrome P450c17α enzyme involved in the synthesis of estrogens and androgens. The 5′ untranslated region of the gene contains a T-to-C polymorphism, which creates an additional Sp1-type (CCACC) promoter motif and has been hypothesized to lead to increased transcriptional activity and enhanced steroid hormone production (51). A Scottish case-control study (52) examined the association between *CYP17* polymorphisms and MBC. Results from this study of 76 MBC patients indicated that the *CYP17* variant allele was found more frequently in breast cancer patients than in controls. The variant genotype associated with higher serum estrogen levels, however, has not been consistently associated with FBC (53, 54). Given that natural levels of estrogen are higher in females than males, Young et al. (52) hypothesized that, in females, any increases might not have a significant effect on breast cancer development beyond already high levels. Correspondingly, Young et al. (52) reasoned that the association between serum estrogen and breast cancer may be detectable only in men. A recent Icelandic study (55) examined the potential role of the T-to-C polymorphism in carriers and noncarriers of the *BRCA2* mutation, where *BRCA2* may play a role in modifying risk of breast cancer. The authors observed that among 39 MBC cases the frequency of the CC genotype was higher among carriers (33.3%) of the 999del5 mutation than noncarriers (16.7%), although this difference did not reach a statistical significance. Although this study does not suggest a major role for the *CYP17* promoter polymorphism in breast cancer risk, one cannot exclude a possible association with breast cancer risk in male *BRCA2* carriers because of the small sample size. Clearly, more evidence is needed to elucidate this suggestive association between *CYP17*and MBC.

Cowden Syndrome. Cowden syndrome is an autosomal dominant cancer susceptibility syndrome characterized by multiple hamartomas and is associated with germ line mutations in the *PTEN* tumor suppressor gene (17). In women, Cowden syndrome is associated with increased risk of breast and thyroid carcinomas as well as many noncancerous lesions. Fackenthal et al. (17) reported two cases of MBC in patients with classic Cowden syndrome phenotypes who also had germ line *PTEN* mutations. The first case occurred in a 41-year-old male with Cowden syndrome and a *PTEN* mutation at c.802delG. The second case occurred in a 43-year-old male with a Cowden syndrome phenotype, including multiple tricheilemmomas and thyroid adenoma. This patient also was a carrier of the c.347-351delACAAT mutation. The authors suggest that germ line *PTEN* mutations seem to contribute to the development of both MBC and FBC within Cowden syndrome families and may be associated with earlier onset of cancer (17).

CHEK2. CHEK2 is a cell cycle checkpoint kinase that mediates cellular responses to DNA damage (56). A protein truncating mutation 1100delC in exon 10 abolishes the kinase function of CHEK2 (57). The *CHEK2**1100delC variant has been associated with risk of FBC in non-*BRCA1/BRCA2* carriers, especially among cases with family history of disease (58). A study by the *CHEK2* Breast Cancer Consortium (59) observed an ~10-fold increased risk of MBC associated with the *CHEK2**1100delC variant in high-risk breast cancer families who do not harbor *BRCA1* or *BRCA2* mutations. The authors suggest that this mutation may account for as much as 9% of breast cancers in men. However, three recent studies (60-62) suggest that the *CHEK2**1100delC variant may not account for as significant a fraction of MBC cases as indicated from the Breast Cancer Consortium study. Syrjakoski et al. (61) observed that 2 of 114 (1.8%) of Finnish MBC cases carried the 1100delC mutation, and Ohayon et al. (60) and Neuhausen et al. (62) observed no carriers of the *CHEK2* mutation among 54 MBC cases from Israel and 188 cases from the United States and United Kingdom, respectively.

Epidemiologic Risk Factors

In addition to the genetic factors associated with an increased risk of MBC, several epidemiologic risk factors have been investigated, including disorders associated with elevated estrogen levels, testicular disorders, benign breast conditions (e.g., gynecomastia), occupational and environmental exposures, and dietary factors.

Endogenous Estrogen Levels. The association between estrogen levels and breast cancer in men is of interest because estrogen-related risk factors have been strongly implicated in the etiology of FBC. Obesity has been implicated in the etiology of MBC due to higher circulating estrogen levels and has fairly consistently been associated with an increased risk of MBC (11, 13, 50, 63-66). For example, Hsing et al. (63) reported that obesity was a significant risk factor for MBC whether evaluated by usual adult weight, body mass index, or perceived overweight. Ewertz et al. (11) also noted increasing risk with increasing height, body weight 10 years before diagnosis, and body mass index 10 years before diagnosis. Other studies have also observed that breast cancer cases were heavier and taller than controls (12, 64). Overall, risk estimates for men in the highest category of weight/body mass index tend to range between 1.63 and 5.45 compared with those in the lowest category. In obese men, estrogen production, metabolism, and bioavailability are enhanced. Levels of circulating estrogens may be increased by aromatization of androgens with conversion of testosterone to estradiol and androstenedione to estrone in peripheral adipose tissue (63). In males, testosterone levels decline with greater body weight, whereas estrogen levels are positively correlated with body weight (13). Sex hormone binding globulin levels also decrease with increasing body weight, so that for any given estrogen level a greater amount is bioavailable in obese men (13). It has been suggested that those men in the highest body weight category may have over a 30% increase in circulating estrogens (63). A methodologic challenge in studying obesity and MBC is the strong correlation between gynecomastia (discussed below) and obesity; thus, it is difficult to distinguish the role of obesity independent of gynecomastia. Serum levels of estradiol are thought to be elevated in males with breast cancer. Sasco et al. (67) in a review of five studies of MBC reported that mean estrogen levels were higher in cases than controls in each study. Urinary estrogen has also been analyzed, but results have been inconsistent (68).

Trans-sexuality has also been implicated in the etiology of MBC. Treatment required to induce male-to-female sexual change include surgical and chemical castration and prolonged administration of large doses of female hormones, especially estrogens (67, 69, 70). Castration may lower androgen levels creating a high estrogen-to-androgen ratio, thus potentially increasing the risk for breast cancer. In a report by Kanhai et al. (70), men chemically castrated for prostate cancer exhibited moderate acinar and lobular formation of the breast tissue, whereas breast tissue in male-to-female trans-sexuals was observed to develop full acinar and lobular formation as a result of combined progestative and estrogenic treatment, thereby simulating a genetic female's breast tissue. Although no analytic epidemiologic evidence is

available, there have been several documented cases of breast cancer among trans-sexuals (69, 71, 72) These cases have been characterized by short latent periods (5-10 years) after exposure before the appearance of the breast tumor (67) and by earlier age at diagnosis (72).

A personal history of prostate cancer has been considered as a risk factor for breast cancer in men. Estrogen therapy is typically used for treatment of prostate cancer and therefore could lead to an increased risk of breast cancer. As stated above in the report by Kanhai et al. (70), after treatment by chemical castration for prostate cancer, there have been observed changes in the breast tissue, which could lead to increased likelihood of development of breast cancer. There have been several case reports of breast cancer cases with a prior history of estrogen therapy for preexisting prostate cancer (67, 73-76). A recent study by Thellenberg et al. (77) examined 137,713 prostate cancer cases and observed a significantly increased risk (standardized incidence ratio, 2.01; 95% confidence interval, 1.44-2.74) of MBC after prostate cancer. One explanation for the association between prostate cancer and MBC is misclassification of the breast cancer, as prostate cancer tends to metastasize to foreign parts of the body and the glandular pattern of metastatic prostate cancer could simulate a primary breast cancer, resulting in a spurious association between prostate cancer and MBC (67, 77-79). Case-control studies have shown no association (8, 65, 80), however, which could be attributed to low statistical power (8, 65, 67, 80). One major difficulty in this area of research is the ability to distinguish between associations with prostate cancer and associations with hormone treatment for prostate cancer. Most studies of prostate cancer and risk of MBC have not collected information regarding hormone treatment.

Another endocrine-mediated condition implicated in MBC etiology is liver cirrhosis. In a recent cohort study, Sorensen et al. (81) reported a 4-fold increase in risk associated with liver cirrhosis and MBC. A study by Lenfant-Pejovic et al. (15) also observed a nonsignificant 3-fold increase in risk of MBC associated with liver cirrhosis. In cirrhosis, there is excessive production of estrogens and a reduction in circulating free testosterone due to elevation of sex steroid binding globulin (15). This hyperestrogenism is considered the likely mechanism that links liver cirrhosis to breast cancer in men (81).

Testicular Disorders. Testicular dysfunction and abnormalities have fairly consistently been reported to be associated with an increased risk of breast cancer. Elevated risk estimates for cryptorchidism (undescended testes) have been reported in several studies (13, 50, 65). Mumps orchitis has also been associated with an elevated risk of MBC (8, 50, 65), although sample size in most studies was too small to obtain statistically significant results. Mumps orchitis is an inflammatory disorder of the testis characterized by swelling. It usually occurs in postpubertal men with a recent history of mumps and may result in testicular atrophy. It may also permanently damage the Leydig and Sertoli cells, the sites of steroid metabolism, and can alter estrogen, androgen, and gonadotropin levels (65). Other testicular disorders, such as orchiectomy (8, 50, 65), congenital inguinal hernia (50, 82), and testicular injury (50, 65), have also been associated with an increased risk of breast cancer. Testicular disorders are often associated with deficient androgen production, which may increase the risk of breast cancer in men (50, 65).

Gynecomastia. Gynecomastia is characterized by enlargement of glandular tissue. It can occur in pubertal boys and men ages >50 years and cirrhotics, after exposure to estrogens (e.g., those given for treatment of prostate cancer), and after treatment with other nonhormonal drugs (e.g., digitalis, cimetidine, reserpine, thiazide, and tricyclic antidepressants; ref. 41, 67). It is also one of the essential features of Klinefelter syndrome due to abnormal hormonal levels involved with this condition (40). For men ages >50 years, gynecomastia is related to the gradual decline in serum testosterone, whereas serum levels of estradiol remain relatively constant, resulting in an estradiol-testosterone imbalance (41). However, gynecomastia may also be related to obesity in men ages >50 years. Gynecomastia as a risk factor for MBC is unclear. Heller et al. (83) reported that 40% of breast cancer patients exhibited microscopic evidence of gynecomastia. Further, autopsy studies have shown gynecomastia to be prevalent in as many as 50% of all MBC patients (84). However, reviews of healthy men have also found gynecomastia to be relatively common (85, 86); therefore, the rates in MBC patients do not seem to be higher than those in the general population (87). In addition, a recent cohort study of 445 men with gynecomastia found no breast cancer cases (88). Risk estimates of the association between gynecomastia and MBC are unstable due to the small sample sizes available. Sasco et al. (67) observed that in several case series the proportion of breast cancer patients with a prior history of gynecomastia varied from 1% to 12.5%. A recent European case-control study of 74 MBC cases and 1,432 population-based controls (89) observed a significant elevation in risk for MBC associated with gynecomastia (odds ratio, 23.42; 95% confidence interval, 4.65-117.97). Difficulties in obtaining the true estimate of men with breast cancer and gynecomastia may be due to recall bias. MBC cases may be more likely than controls to remember other breast conditions due to enhanced awareness of their breasts. The result might be reduced reporting of gynecomastia by males without breast cancer. Furthermore, spurious associations could be the result of diagnostic bias.

Occupational and Environmental Exposures. Recent attention has been placed on the role of occupational and environmental factors in the development of MBC and especially on the role of exposure to electromagnetic fields (EMF) and light at night. A proposed mechanism is that EMF exposure may affect pineal gland activity, which leads to decreased production of melatonin (90). As reviewed by Brainard et al. (91), the majority of animal studies have shown that when pineal gland function is disrupted there are increases in breast tumor incidence, multiplicity, or size. There is also *in vitro* evidence that melatonin blocks estrogen-induced proliferation of human breast cancer cells (91).

Of the case-control studies investigating MBC risk and exposure to EMFs, most show no association (11, 92-96). However, a study by Demers et al. (97) using population-based cancer registries reported an increased risk in breast cancer for men who worked in any job with EMF exposure. The risk was highest among electricians, telephone linemen, and electric power workers.

Similarly, most of the cohort studies show no significant effect of EMF exposure or of working in an electrical occupation on risk of breast cancer (98-105). Several other cohort studies were not able to assess the association between EMF and breast cancer risk as no cases of MBC were obtained (106-110). A study by Tynes et al. (111) did report a significant 2-fold risk elevation for Norwegian workers exposed to EMFs. A Swedish study by Floderus et al. (112) also noted a 5-fold risk elevation for workers highly exposed to EMF. A recent meta-analysis pooled all the calculable risk estimates for an overall pooled estimate of 1.37 (95% confidence interval, 1.11-1.71), suggesting that exposures to EMFs may be associated with a modest excess risk of breast cancer in men (113).

Two major problems exist that hamper occupational studies of EMF exposure and breast cancer risk. First is that MBC is extremely rare, and many studies were not sufficiently powered to detect an association if one truly exists. The second problem relates to misclassification of the exposure. Many studies do not directly measure EMF exposure and only obtain information on job titles as a proxy measure of exposure to EMFs. Some studies examine residential exposures (93),

which tend to be quite low and often do not account for other EMF sources, whereas other studies are of higher occupational exposures (92, 94, 97, 111), resulting in a wide range of exposures and doses to evaluate and thus may lead to errors in the categorization of EMF exposures. If the misclassification is random or nondifferential, then the risk estimates will tend to be biased toward the null and little or no effect may be seen.

Occupational exposure to high temperatures has also been associated with increased risk of breast cancer in men presumably due to testicular damage incurred by increased temperature (92), which in turn may lead to altered levels of circulating androgen and estrogen. Several studies have reported increased risk estimates for exposure to high temperatures (15) and for occupations, such as workers in blast furnaces, steel work, rolling and finishing mills, machinery repair, and manufacturing of motor vehicles (65, 92, 95, 105). However, workers in these fields may be exposed to other potential carcinogens in addition to high temperatures, such as polycyclic aromatic hydrocarbons (PAH), nitrogen oxides, nitrosamines, and metal fumes (92), making it difficult to determine if the excess risk is due to exposure to the high temperature itself or due to exposure to some other potential carcinogen.

Few studies have examined PAH exposure and occupation, the results of which are inconsistent (15, 92, 114). PAH adduct levels have been found to be increased in FBC tissue compared with those who are cancer free (115). A study by Hansen (114) found a significant increased risk for MBC among workers who were potentially exposed to automotive gasoline and combustion products (PAHs) when compared with other employees. Risk was also significantly associated with duration of occupational PAH exposure. Lenfant-Pejovic et al. (15) found a slight nonsignificant increased risk in men exposed to gasoline and grease, whereas Cocco et al. (92) found no association of risk of MBC and occupational exposure to either PAHs or organic solvents.

Radiation exposure has been shown to increase risk of MBC. Exposure to ionizing radiation in men seems to produce a similar degree of risk for breast cancer as in women who were irradiated during puberty, although the absolute risk for women would be quite different (41, 116). The latent period for men exposed to radiation is ~20 to 30 years (116). In addition to case reports of breast cancer occurring in men exposed to radiation (8, 117, 118), several studies have shown that the risk of breast cancer is increased in men exposed to repeated and prolonged chest flouroscopies and for increased frequency of chest X-rays (13, 116, 118, 119).

Dietary Risk Factors. Although there is a comprehensive literature on the nutritional epidemiology of FBC, few studies have addressed dietary factors in MBC. Meat consumption has been considered as a risk factor for many different cancers. A few studies have addressed meat consumption and risk of MBC, the results of which are inconclusive. Results from a small Chinese case-control study (120) indicated that meat intake was associated with a 6-fold increase in risk of MBC. However, misclassification could have affected the risk estimate in this study as most information collected regarding cases was obtained from surrogates. A study by Hsing et al. (63) also noted a nonsignificant increase in risk for those men who consumed red meat seven or more times per week. However, in a U.S. investigation, Rosenblatt et al. (121) showed no evidence for an association between MBC and consumption of beef, pork, fish, or total dietary fat.

Evidence for a protective association between fruit and vegetable intake and MBC risk is also inconsistent. Two studies (63, 120) have observed results suggestive of a protective effect for fruit and vegetable consumption, whereas a third study (121) found no association.

Alcohol intake has been thought to contribute to FBC because of the influence of alcohol on hormone levels (122), and recent research has shown an association between alcohol intake and FBC (123-125). Two studies of chronic alcoholics (80, 82) noted a 2-fold increase in risk in MBC, and a recent European population-based case-control study (89) observed an ~6-fold increase in risk in the highest alcohol exposure category (>90 g alcohol/d) compared with light drinkers and nondrinkers. The authors also observed that the risk increased by 16% for each increment of 10 g alcohol/d. However, a study of male alcoholics in Sweden (126) observed no association. Other studies examining the relationship between levels of alcohol consumption and risk of MBC did not observe any significant associations (50, 63, 121). One difficulty in examining individuals with high alcohol consumption is the possible confounding effect of liver cirrhosis on the results.

There seems to be little evidence at this time to suggest that dietary habits are a major contributor to breast cancer in men.

Table 1. Risk factors for MBC

Known	Suggestive	Inconclusive
BRCA2	Cowden syndrome	*AR* gene
Family history	Cirrhosis	*CHECK2*
Klinefelter syndrome		Prostate cancer
Obesity		Prostate cancer treatment
Testicular disorders		Gynecomastia
Cryptorchidism		Occupational exposures
Mumps orchitis		EMFs
Orchiectomy		PAHs
Radiation exposure		High temperatures
Exogenous estrogen		Diet
		Alcohol

Summary

Establishment of risk factors for MBC is made difficult by the paucity of research on this topic and the methodologic challenges facing research in this area. It is often difficult to draw conclusions about causality due to the rarity of the disease and the small sample size of studies. Even so, several risk factors for MBC have been elucidated (Table 1).

Similar to FBC, genetics seems to play an important role in MBC. *BRCA2* mutations seem to be associated with the majority of inherited breast cancer in men. In addition, family history of breast cancer and Klinefelter syndrome are consistently associated with MBC. The relationship between the *AR*, *CYP17*, *PTEN*, and *CHEK2* genes and MBC are inconclusive.

The most frequently examined epidemiologic risk factors for MBC include disorders associated with increased estrogen levels, testicular disorders, gynecomastia, occupational and environmental exposures, and dietary factors. Those risk factors that seem to be consistently associated with MBC include obesity, testicular disorders (e.g., cryptorchidism, mumps orchitis, and orchiectomy), and radiation exposure. The associations between risk factors such as prostate cancer, trans-sexuality, liver cirrhosis, dietary risk factors, and exposure to EMFs, PAHs, or high temperatures remain inconclusive, and further investigation into these factors is warranted.

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Epidemiology of Male Breast Cancer

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