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Etiologic Factors for Male Breast Cancer in the U.S. Veterans Affairs Medical Care System Database

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Abstract

The etiology of male breast cancer is largely unknown, reflecting its relative rarity. Although a number of previous studies have suggested relationships with a variety of medical conditions, the results have largely derived from case-control studies and may reflect recall biases. Within the large U.S. Veterans Affairs computerized medical care system database, we had the opportunity to access 26 million hospitaldischarge records over the period 1969–1996 and to relate various documented medical conditions to the risk of subsequent male breast cancer. This allowed us to calculate relative risks (RR) and 95% confidence intervals (CI) for male breast cancer associated with conditions occurring one or more years after initial hospitalization, adjusted for age, race, calendar year, duration of follow-up, and number of hospital visits. Among 4,501,578 men aged 18–100 years, a total of 642 cases of primary male breast cancer were identified (523 among whites, 119 among blacks). Medical conditions that were significantly related to risk were 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 syndrome (29.64, 12.26–71.68), and gynecomastia (5.86, 3.74–9.17). Additionally, among black patients, cholelithiasis emerged as a significant risk predictor (3.45, 1.59–7.47). Diseases that have previously been related to male breast cancer risk that were not supported by our study results included thyroid diseases, smoking-related conditions, liver cirrhosis, prostatic hyperplasia, and fractures. After adjustment for obesity, the association with diabetes disappeared, but that with gynecomastia persisted. In multivariate models that simultaneously considered all important medical predictors of risk, significant risks were seen for Klinefelter syndrome (16.83, 6.81–41.62), gynecomastia (5.08, 3.21–8.03), obesity (1.91, 95% CI 1.50–2.44) and orchitis/epididymitis (1.80, 1.08–3.01). These results support previous speculations that male breast cancer is influenced not only by tissue at risk, but also by hormonal and inflammatory factors.

Keywords

Male breast cancer; medical history; hormonal factors

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Introduction

Male breast cancer is uncommon, with an occurrence less than one percent that of female breast cancer (1). The most recent statistics indicate that approximately 1,990 men will develop breast cancer in the U.S. in 2008, and that 450 will die as a result of the disease.

As a result of its rarity, relatively little is known regarding the etiology of male breast cancer. Descriptive studies document that, unlike female breast cancer, there is no evidence of a plateauing of rates after age 50 (resulting in relatively late average ages at onset) and that incidence is higher for blacks than whites (2,3). Analytic studies have been uncommon, and mostly of case-control designs, raising questions regarding the possibility that identified risk factors reflect the influence of selection or recall biases.

Similar to female breast cancers, many of the identified risk factors for male breast cancer suggest the importance of hormonal factors. Patients with Klinefelter syndrome, a condition characterized by a rare chromosomal abnormality of 47 XXY karyotype and notable hormonal alterations, are known to have an over 50-fold increases in risk (4,5). Elevated risks of male breast cancer have also been related to a variety of other conditions associated with altered endogenous hormones, including obesity (6–10), diabetes (8,11), liver cirrhosis (12,13), hyperthyroidism (12), gallstones (12), and bone fractures (6). In addition, like female breast cancer, studies have suggested that high rates of disease may relate to high intakes of alcohol (14–16) and to limited physical activity levels (6), both behaviors that have been shown to influence endogenous hormone levels.

Because many of the risk factors that have been suggested for male breast cancer are medical conditions, we conducted an analysis within the US Veterans Affairs medical care system database, a large resource in which medically documented inpatient admissions could be evaluated in relation to male breast cancer.

Methods

We analyzed records for males in the Patient Treatment File from the US Veterans Affairs medical care system. A description of the system has been published previously (17). The dates of records we used ranged from July 1, 1969 to September 30, 1996. The initial study population consisted of 26 million hospitaldischarge records from almost 6 million veterans with at least onehospital visit. We excluded 491,588 records for prevalent cancers (cancer on first admission), 203,513 records for subjects who died on their first admission, 135,651 records with races other than black or white, 112,527 records for females, and 2,969 records from patients under 18 years of age or older than 100. We also excluded 94,082 patients who were non-veterans and 371,129 patients who did not survive one year of follow-up (this includes patients who developed cancer in that first year). Thus, the current analysis was based on records from 4,501,578 males contributing to 53,654,181 person-years of risk (Table 1). We followed eligible subjects until they obtained a diagnosis of cancer, died, or reached the end of the observation period (September 30, 1996).

Cases of male breast cancer and other conditions that we speculated might be related to breast cancer development were coded using the International Classification of Diseases eighth or ninth versions (ICDA-8 and ICD-9CM), depending on the date of the diagnosis; records before 1981 used codes from ICDA-8 and those after used codes from ICD-9CM. All men with codes of 174 in ICDA-8 and 175 in ICD-9 were considered as male breast cancer cases in this study.

We calculated age-adjusted relative risks (RRs) and 95%confidence intervals (CIs) using the Poisson regression procedure, AMFIT, in Epicure (version1.4 [2002]; HiroSoft International Corp, Seattle, WA) to determine the risk of male breast cancer associated with different medical

conditions in white and black men. RRs were adjusted for attainedage (< 40, 40–49, 50–59, 60–69, 70–79, and > 79 years), attained calendar year (1969–1974,1975–1979, 1980–1984, 1985–1989, and 1990–1996), latency between study entry and study exit (2–3, 4–5, 6–9,10–14, and > 14 years), number of hospital visits (<3, 3–4, and 5 or more visits), and race (white or black). Initial models contained one medical condition to test the effect that specific condition had on breast cancer risk. The final model contained all conditions that initially modified breast cancer risk ($p<.05$).

We were exempt from review by the National Institutes of Health (NIH) Office of Human Subjects Research Institutional Review Board (IRB) because the derived data were anonymized and we had no contact with patients.

Results

During 53,654,181 years of follow-up, 642 male breast cancers were identified among the 4,501,578 patients studied (Table 1). The median age at study entry for non-cases was 52.5 years, while the mean years of followup was 11.7. Approximately 18% of the cases occurred among blacks, who presented with a slightly earlier age at diagnosis (65.9 years) than whites (66.3 years).

Of the various conditions examined (Table 2), the one that most strongly related to male breast cancer risk was Klinefelter syndrome, which was associated with a RR of 29.64 (95% CI 12.26–71.68), based on 5 observed cases. The risk was higher for blacks (93.3) than whites (20.24), although there was considerable instability and overlap in these risks.

Other conditions associated with increased risk of all male breast cancers included endocrine, nutritional, metabolic and immunity disorders (1.34, 1.13–1.60), diabetes (1.30, 1.05–1.60), obesity (1.98, 1.55–2.54), orchitis/epididymitis (1.84, 1.10–3.08), and gynecomastia (5.86, 3.74–9.17). The magnitude of risk associated with endocrine and other disorders and diabetes varied little by race, although they were significant only among whites. An elevated and significant relationship for obesity was restricted to whites (RR=2.12, 1.63–2.75), whereas the orchitis/epididymitis association was significant only among blacks (2.97, 1.21–7.32). Noteworthy conditions that were unrelated to risk were alcoholism (0.90), disorders of the thyroid glands (1.20), chronic obstructive pulmonary disease (0.89), liver diseases due to alcoholism (0.96), other liver diseases (1.02), hyperplasia of the prostate (1.05), osteoporosis (0.89), and fractures (1.02).

Several conditions that were not observed overall emerged as significant predictors of male cancer risk within the racial subgroups. Although based on small numbers, significantly high risks of male breast cancer among blacks were seen for disorders of the parathyroid, pituitary, thymus and adrenal glands (4.87, 1.78–13.30, based on 4 cases) and cholelithiasis (3.45, 1.59–7.47, 7 cases).

When those conditions that showed significant relationships with risk were stratified by follow-up time (2–5 years, >5 years), there were no consistent patterns by time for diabetes, obesity or orchitis/epididymitis (Table 3). The risk associated with gynecomastia was highest for the subjects diagnosed with breast cancer within 2–5 years (13.45, 6.90–26.26), but a significant risk was also seen for those diagnosed with breast cancer more than 5 years later (3.96, 2.17–7.21). For cholelithiasis, a significant risk of breast cancer emerged more than 5 years later (1.57, 1.04–2.36), with an even further enhanced risk among black men (3.12, 1.25–7.79). Among the men with Klinefelter Syndrome, all diagnoses of breast cancer occurred more than 5 years later, resulting in an overall RR of 33.91 (14.01–82.08) and a RR of 102.8 (24.94–423.6) when analyses were restricted to blacks.

When cancer risks were examined according to the ages at which conditions were first noted as inpatient admissions (<50, ≥50 years), there was little variation for most conditions. Orchitis/epididymitis with first admission at age 50 or older was associated with a slightly stronger relationship with male breast cancer risk (1.98) than earlier admissions (1.41). The same was true for Klinefelter syndrome, which was associated with RRs of 42.63 for those admitted at age 50 or older and 13.31 for medical admissions at younger ages.

The relationship with diabetes was attenuated and became non-significant after adjustment for obesity admissions. In multivariate analyses in which all medical conditions that persisted in significant risk relationships were adjusted for each other (Table 4), associations were seen with obesity (1.91, 1.50–2.44), orchitis/epididymitis (1.80, 1.08–3.01), gynecomastia (5.08, 3.21–8.03), and Klinefelter syndrome (16.83, 6.81–41.62) (Table 4). Among blacks, a significant relationship with cholelithiasis persisted (3.44, 1.59–7.46) that was not observed among whites.

Discussion

The Veterans Affairs medical system database offered a unique opportunity for assessing medical conditions related to male breast cancer risk. Within this population of over 4.5 million patients, we were able to relate documented occurrences of a variety of medical conditions to over 600 cases of a very rare disease. Unique characteristics of this patient population allowed opportunities for evaluating relationships with many conditions that previous investigations have been unable to assess in detail, particularly a variety of conditions of interest given their effects on endogenous hormones.

The medical condition that was most strongly associated with male breast cancer risk in our patient population was Klinefelter syndrome, a relationship well established in other investigations (4,5,18,19). The prevalence of the condition in our population of male breast cancer cases was considerably lower than that of 7.5% noted in a Swedish study (4), undoubtedly reflecting our focus on individuals who were medically qualified to enter military service and be eligible for VA benefits. However, our RR of nearly 30 compares well with that estimated in the Swedish study (4,5), as well as in another investigation in the UK (4,5). Adjustment for other medical predictors decreased this risk to a RR of 17, but this was not due to confounding by gynecomastia--a condition often associated with Klinefelter syndrome (20)--since no patients in our study had both diagnoses. In terms of a biologic explanation, Kleinfelter patients have low levels of testosterone and high levels of estrogens (21), resulting in a high estrogen/androgen ratio, which could in turn lead to abnormal hormonal stimulation of cell proliferation in mammary ductal epithelium (20). The association could also reflect treatment with exogenous testosterones (21), which could be converted to estrogens in peripheral adipose tissue.

Gynecomastia has long been associated with the detection of male breast cancer (22–24), although its relevance as an etiologic factor has been questioned (25). It has been postulated that it might affect risk through providing increased tissue at risk, but it is also possible that surveillance issues or uncontrolled confounding for other important medical predictors of male breast cancer (e.g., obesity) could be involved. Our finding that male breast cancer risk was higher among men with recent admissions for gynecomastia may suggest some effect of surveillance bias, though persistently increased risks for those followed for more than five years lends support to a true biologic relationship. It was also noteworthy that the association with gynecomastia was altered little by adjustment for obesity, suggesting independent relationships with the two conditions.

The importance of adiposity in the etiology of male breast cancer is emphasized by elevated risks associated with obesity that have been found in both retrospective (7–10) and prospective (6) studies. We found a 2-fold increased risk associated with an inpatient admission for obesity, a relationship that persisted after adjustment for such correlated medical diagnoses as diabetes. Although our study considered only the extremes of obesity, namely inpatient admissions, more generalized obesity in men has been associated with decreased testosterone (26–28) and sex hormone-binding globulin (26,28) levels but increased estrogen levels (29–31), and therefore greater estrogen bioavailability. However, obese individuals also often have gynecomastia, which could affect risk through increased tissue at risk. However, as noted, we saw little evidence for an alteration in risk associated with obesity after adjustment for gynecomastia, further supporting an important role for hormonal influences in the etiology of male breast cancer.

Previous investigations have suggested an increased risk of male breast cancer among diabetics (8,11), of interest given that male diabetics have low testosterone levels (32). However, these studies have been unable to adjust for the correlated variable of obesity. It was therefore of interest that our initial finding of an elevated risk associated with an admission for diabetes failed to persist after we adjusted for obesity admissions. This finding is consistent with several other recent studies that have failed to find an independent effect of diabetes on male breast cancer risk (6).

Excessive alcohol intake has been suggested to increase male breast cancer risk because of its influence on hormone levels (33). Several (15,16), although not all (34), studies of chronic alcoholics have noted an increased risk of male breast cancer. Although one case-control study showed an elevated risk of male breast cancer associated with high alcohol intake levels (14), other epidemiologic investigations (6,9,11,35), including a recent prospective investigation (6,9,11,35), have not confirmed the association. Despite fairly large numbers of VA patients with an admission diagnosis of alcoholism, we found no evidence of any alteration in male breast cancer risk in any subgroups examined.

Similarly, we failed to detect an association with liver cirrhosis that was due to either alcohol consumption or other causes. Thus, although some previous studies have found cirrhosis related to male breast cancer risk (12,13) and the relationship is biologically feasible given that there is an excessive production of estrogens and a reduction in circulating free testosterone due to elevated sex steroid hormone binding globulin (12), we found no evidence for a link between the two diseases. Based on null findings for chronic obstructive pulmonary disease (COPD), a well-known condition related to smoking, we, like others (36–38), failed to find evidence for male breast cancer risk being influenced by cigarette smoking.

Given that several epidemiologic studies have found associations of male breast cancer risk with late puberty (11); being single, infertile, or childless (7,9,11,12,36); and undescended testes, testicular trauma or infections causing orchitis (11,37), we also examined risk in relation to a variety of male genital and urogenital disorders. Although we could not evaluate previous suggestions of an increased risk of male breast cancer associated with a personal history of prostate cancer (39,40) because of our reliance on a initial diagnosis of cancer to define cases of male breast cancer in this study, we found no support that either prostatic hypertrophy or dysplasia were associated with risk. We did, however, observe a significant association of male breast cancer risk with a history of orchitis or epididymitis. Although the condition is often associated with gynecomastia, only one patient in our study had both diagnoses. Mumps orchitis has previously received attention as a risk factor for male breast cancer given that it can permanently damage Leydig and Sertolig cells and alter estrogen, androgen, and gonadotropin production (20). Given that it also associated with a variety of inflammatory processes, immunologic factors could also be involved.

Our study also had an opportunity to evaluate relationships with several other diseases that have been suggested as related to male breast cancer risk. This included a recent observation of a link with bone fractures, hypothesized as affecting male breast cancer through an imbalance of bioavailable estrogens to testosterone (6). However, our analysis found no substantial alterations in risk with either fractures at various sites or with osteoporosis, a condition also associated with altered hormone levels. We also found no relationships with a variety of thyroid diseases, of interest given that at least one prior study suggested a potential association between hyperthyroidism and male breast cancer risk (12). However, similar to one investigation (12), we observed a significant association with cholelithiasis, an association seen only among black men. Although chance cannot be ruled out as a potential explanation to this finding, it is well recognized that estrogens increase biliary cholesterol secretion causing cholesterol supersaturation of bile ducts (41)and the formation of stones (42). Higher estrogen levels among patients with gallbladder stones might therefore provide a possible biologic mechanism for a relationship with male breast cancer, supporting the need for further scrutiny.

Although this investigation had a number of strengths, including its large size and medically documented diagnoses of a wide variety of conditions, it also had various limitations. This included lack of detailed information on clinical characteristics of the male breast cancer. Further, subjects were not directly interviewed, precluding examination of non-medical conditions hypothesized as affecting risk, including familial and genetic factors (20). Presumably though, as with female breast cancer, genetic influences would be responsible for only a small proportion of disease occurrence, with environmental factors playing a much larger role. However, we also lacked information on some environmental factors that could have confounded our observed relationships, including medical and occupational radiation, diet, physical activity, use of tobacco and alcohol, and occupational factors that have previously been related to male breast cancer risk (20,25). Our information on medical conditions also was dependent on hospitalization data, which would have affected the prevalence (and possibly risk associations) for conditions that rarely result in a hospitalization (e.g., obesity, fractures) or that resulted in hospitalization outside of the VA medical care system. Given the large size of the database, we also need to accept that there may have been errors and incomplete information, which hopefully would have been compensated by the large size of the study population. Multiple comparisons could also have results in chance findings.

In sum, this study observed and confirmed some important medical predictors of male breast cancer risk, including relationships with Klinefelter syndrome, obesity, gynecomastia, orchitis/epididymitis, and possibly cholelithiasis. The relationship with gynecomastia supports the importance of susceptible epithelial tissue. However, given the independent role of the other identified medical conditions, additional biologic mechanisms merit attention, including relationships with hormonal (altered bioavailable estrogen levels) and immunologic factors.

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Table 1

Characteristics of the Study Population (US Veterans Administration Inpatient Hospitalization Database): White and Black Male Veterans With at Least One Hospital Admission Between July 1, 1969, and September 30, 1996 Who Were Followed for at Least One Year

	White		Black		All Subjects	
Characteristics	**Male breast cancer**	**No male breast cancer**	**Male breast cancer**	**No male breast cancer**	**Male breast cancer**	**No male breast cancer**
No. of patients	523	3,668,721	119	832,215	642	4,500,936
Median age at study entry	58.1	53.5	57.9	47.7	58.1	52.5
Mean years of follow up	7.8	11.7	7.7	11.9	7.8	11.7
Person years at risk	4,065	42,760,624	911	9,888,582	4,976	52,649,205
Median number of hospital visits	4	3	4	3	4	3
Median age at breast cancer diagnosis	66.3	-	65.9	-	66.1	-

Table 2

Relative Risks of Male Breast Cancer Associated with Previous Personal Histories of Selected Medical Conditions, U.S. Veterans Administration Inpatient Hospitalization Database, 1969–1996

		White			Black			All Subjects		
Condition	**ICD-9 codes**	**N**	**RR**	**95% CI**	**N**	**RR**	**95% CI**	**N**	**RR**	**95% CI**
Alcoholism	291,303,535.3,571.0–572.3,980	103	0.95	0.76–1.19	19	0.67	0.40–1.13	122	0.90	0.73–1.10
Disorders of thyroid glands	240–246	11	1.21	0.66–2.20	2	1.15	0.28–4.66	13	1.20	0.69–2.08
Goiter	240–241	4	2.27	0.85–6.07	1	1.69	0.24–12.15	5	2.15	0.89–5.19
Thyrotoxicosis with or without goiter	242	2	0.87	0.22–3.48	0	0.00		2	0.69	0.17–2.76
Acquired hypothyroidism	244	5	0.88	0.36–2.12	1	1.45	0.20–10.46	6	0.93	0.42–2.09
Endocrine, nutritional and metabolic diseases, and immunity disorders	240–279	171	**1.33**	1.10–1.61	43	1.37	0.92–2.02	214	**1.34**	1.13–1.60
Diabetes	250	86	**1.28**	1.01–1.62	25	1.35	0.86–2.12	111	**1.30**	1.05–1.60
Parathyroid, pituitary, thymus, adrenal glands	252–255	3	0.95	0.31–2.97	4	**4.87**	1.78–13.30	7	1.77	0.84–3.73
Obesity	278	68	**2.12**	1.63–2.75	7	1.27	0.59–2.75	75	**1.98**	1.55–2.54
Chronic obstructive pulmonary disease	490, 491, 492, 493, 494, 495, 496	86	0.87	0.69–1.10	14	1.09	0.62–1.93	100	0.89	0.72–1.12
Acute and subacute necrosis of liver, chronic liver disease and cirrhosis, liver abscess and sequelae of chronic liver disease, other disorders of liver	570–573	28	0.97	0.66–1.43	3	0.44	0.14–1.41	31	0.87	0.61–1.26
Alcoholic fatty liver, acute alcoholic hepatitis, alcoholic cirrhosis of liver, alcoholic liver damage unspecified	571.0	23	1.04	0.68–1.58	3	0.60	0.19–1.91	26	0.96	0.64–1.42
Non-alcoholic cirrhosis: chronic hepatitis, cirrhosis of liver without mention of alcohol, biliary cirrhosis, other chronic nonalcoholic liver disease, unspecified chronic liver disease without mention of alcohol	571.8–571.9	5	1.00	0.42–2.43	1	1.07	0.15–7.66	6	1.02	0.45–2.27
Cholelithiasis	574	22	1.17	0.76–1.80	7	**3.45**	1.59–7.47	29	1.39	0.96–2.03
Diseases of the male genital organs	600–608	103	1.11	0.89–1.39	25	1.22	0.77–1.93	128	1.13	0.92–1.39

		White			Black			All Subjects		
Condition	**ICD-9 codes**	**N**	**RR**	**95% CI**	**N**	**RR**	**95% CI**	**N**	**RR**	**95% CI**
Hyperplasia of prostate	600	72	1.03	0.79–1.33	17	1.16	0.67–1.98	89	1.05	0.83–1.33
Inflammatory disease of prostate	601	14	1.17	0.69–2.00	4	1.57	0.58–4.28	18	1.24	0.77–1.99
Orchitis and epididymitis	604	10	1.54	0.82–2.89	5	**2.97**	1.21–7.32	15	**1.84**	1.10–3.08
Gynecomastia	611.1	14	**5.19**	3.04–8.85	6	**8.41**	3.68–19.24	20	**5.86**	3.74–9.17
Osteoporosis	733	5	0.63	0.26–1.51	3	3.10	0.97–9.88	8	0.89	0.44–1.80
Klinefelter syndrome	758.7	3	**20.24**	6.49–63.16	2	**93.3**	22.6–385.2	5	**29.64**	12.26–71.68
Fractures	800–829	49	1.03	0.76–1.38	8	0.96	0.46–1.99	57	1.02	0.77–1.34
Fracture of skull	800–804	9	1.52	0.78–2.94	1	0.72	0.10–5.20	10	1.37	0.73–2.57
Fracture of neck and trunk	805–809	15	0.99	0.59–1.66	3	1.46	0.46–4.61	18	1.05	0.66–1.69
Fracture of upper limb	810–819	9	0.74	0.38–1.44	1	0.52	0.07–3.76	10	0.72	0.38–1.34
Fracture of lower limb	820–829	20	0.85	0.54–1.33	6	1.50	0.66–3.44	26	0.94	0.64–1.40

Abbreviations: ICD-9, International Classification of Diseases, ninth revision; RR, relative risk; CI, confidence interval. All analyses were adjusted for age, calendar time, race, latency, and number of number of hospital visits.

Table 3

Relative Risks for Male Breast Cancer by Interval Between Diagnosis and Hospital Admission of Previous Medical Conditions and by Age at Onset of Previous Medical Conditions, U.S. Veterans Administration Inpatient Hospitalization Database, 1969–1996

	Interval Between Condition of Breast Cancer						By Age at Diagnosis of Condition					
	2–5 yrs			>5 yrs			<50			≥50		
	N	RR	95% CI	N	RR	95% CI	N	RR	95% CI	N	RR	95% CI
Diabetes	31	1.13	0.77–1.65	80	**1.39**	1.08–1.78	22	1.37	0.86–2.19	89	**1.27**	1.01–1.61
Obesity	19	**2.26**	1.41–3.64	56	**1.90**	1.43–2.53	23	**2.20**	1.40–3.47	52	**1.91**	1.42–2.55
Chronic obstructive pulmonary disease	33	1.14	0.78–1.7	67	0.81	0.62–1.06	18	0.84	0.50–1.40	82	0.91	0.72–1.16
Cholelithiasis	4	0.89	0.33–2.39	25	**1.57**	1.04–2.36	6	1.45	0.63–3.31	23	1.39	0.91–2.12
Orchitis and epididymitis	5	**3.18**	1.31–7.73	10	1.51	0.80–2.83	3	1.41	0.45–4.42	12	**1.98**	1.12–3.53
Gynecomastia	9	**13.45**	6.90–26.26	11	**3.96**	2.17–7.21	5	**5.60**	2.28–13.73	15	**5.95**	3.55–9.97
Klinefelter syndrome	0	-	-	5	**33.91**	14.01–82.08	1	**13.31**	1.86–95.43	4	**42.63**	15.88–114.50

Table 4

Multivariate Adjusted Relative Risks for Male Breast Cancer Associated with Significant Medical Predictors of Risk, U.S. Veterans Administration Inpatient Hospitalization Database, 1969–1996

	Whites			Blacks			All Subjects		
	N	**RR**	**95% CI**	**N**	**RR**	**95% CI**	**N**	**RR**	**95% CI**
Obesity	68	**2.06**	1.59–2.68	7	1.17	0.54–2.55	75	**1.91**	1.50–2.44
Cholelithiasis	22	1.12	0.73–1.72	7	**3.44**	1.59–7.46	29	1.35	0.92–1.96
Orchitis and epididymitis	10	1.51	0.80–2.82	5	**3.02**	1.22–7.44	15	**1.80**	1.08–3.01
Gynecomastia	14	**4.63**	2.69–7.96	6	**6.50**	2.66–15.84	20	**5.08**	3.21–8.03
Klinefelter syndrome	3	**12.09**	3.80–38.44	2	**43.38**	9.46–199.10	5	**16.83**	6.81–41.62