Published in final edited form as:
Acta Paediatr. 2011 June ; 100(6): 814–818. doi:10.1111/j.1651-2227.2010.02131.x.

Breast Cancer Risk Among Klinefelter Syndrome Patients

Louise A. Brinton, Ph.D.
Hormonal and Reproductive Epidemiology Branch Division of Cancer Epidemiology and Genetics National Cancer Institute 6120 Executive Boulevard, Room 5018 Rockville, MD 20852-7234 brinton@nih.gov Telephone: 301-496-1693 Facsimile: 301-402-0916

Abstract

Aim—To evaluate male breast cancer (MBC) risk among Klinefelter Syndrome (KS) patients and relate this to possible biologic explanations.

Methods—A literature review was conducted to identify case series and epidemiologic studies that have evaluated MBC risk among KS patients.

Results—Case reports without expected values have often led to false impressions of risk. Problems include that a diagnosis of cancer can prompt a karyotypic evaluation and that many cases of KS are unrecognized, resulting in incomplete denominators. Few carefully conducted epidemiologic studies have been undertaken given that both KS and male breast cancer are rare events. The largest study found 19.2- and 57.8-fold increases in incidence and mortality, respectively, with particularly high risks among 47,XXY mosaics. These risks were still approximately 30% lower than among females, contradicting case reports that KS patients have breast cancer rates similar to females. Altered hormone levels (especially the ratio of estrogens to androgens), administration of exogenous androgens, gynecomastia, and genetic factors have been offered as possible explanations for the high risks.

Conclusions—Additional well-designed epidemiologic studies are needed to clarify which KS patients are at a high risk of developing MBC and to distinguish between possible predisposing factors, including altered endogenous hormones.

Keywords

Genetics; gynecomastia; hormones; Klinefelter syndrome; male breast cancer; risk

Introduction

In 1942, Harry F. Klinefelter described a syndrome characterized by gynecomastia, small testes, complete spermatogenic failure, Leydig cell insufficiency, and increased excretion of follicle-stimulating hormones (FSH). Such patients were subsequently discovered to have the sex chromosome genotype of 47,XXY, and the condition became known as Klinefelter syndrome (KS). In addition to hypogonadism, KS has been found to be characterized by various physical, developmental and hormonal alterations, including decreased androgen to estrogen levels. There have been a number of reports of male breast cancer (MBC) occurring among KS patients, prompting an interest in further characterizing and understanding underlying biologic mechanisms.

Although it is now recognized that KS patients have elevated rates of MBC, the magnitude of the relationship remains uncertain. Few epidemiologic studies have been conducted, and most have been plagued by small numbers or surveillance and selection biases. We reviewed the relevant literature, assessing strengths and limitations of the investigations. Findings were related to biologic correlates to add insights into possible mechanistic pathways.

Methodologic Difficulties Involved in Assessing Cancer Risks Among KS Patients

Clinical reports of MBCs developing among KS patients are difficult to interpret given the absence of a comparison group and inability to derive expected values. In some studies, the strength of the association appears enhanced because a cancer diagnosis leads to a karyotypic evaluation and the diagnosis of KS. Further problems arise as a result of under-recognition of KS on a population basis.

Epidemiologic studies are required to derive conclusions regarding the true extent of risk, but these are difficult to undertake, and can have inherent methodologic limitations. For instance, case-control studies, which compare exposures between individuals with and without a condition (e.g., MBC), usually depend on patient reports of exposures (e.g., the prior diagnosis of KS) and involve small numbers of pertinent events.

Another approach is to undertake a cohort investigation, which assesses cancer risk subsequent to a diagnosis of KS. To enable the assessment of cancers that generally occur at older ages (such as is the case for MBC), the most feasible approach is a retrospective cohort study, whereby a cohort of patients with KS is assembled from historical records, allowing subsequent assessment of development of cancers.

A difficulty faced by retrospective cohort studies, however, is the fact that a sizeable proportion of KS patients are never diagnosed with the condition. A presumptive clinical diagnosis will prompt cytogenetic studies. Therefore, subjects who are assessed for cancer risk are usually biased towards having greater degrees of clinical abnormalities. In the largest study conducted (1), phenotypic abnormalities were admittedly over-represented. Further, this study did not include patients with mosaicism associated with Down syndrome trisomies because of its recognized link with cancer, further limiting the generalizability of the results.

The final difficulty in assessing the relationship of KS to MBC risk is in assembling sufficient numbers of each condition for investigation. KS is grossly under-diagnosed, with approximately 7 out of every 10 cases being unrecognized, for a prevalence at birth of only 1 in every 660 male males(2). Thus, it difficult to assemble sufficiently sized cohorts to evaluate subsequent cancer risk, particularly for MBC, which has an estimated lifetime occurrence of 1 in every 1,000 individuals (3). MBC is also a condition that is usually not diagnosed until the mid sixties or seventies, requiring long-term follow-up of patients.

Case Series

The association of MBC with KS was first suggested by Bauer and Erickson in 1955 (4). Subsequent reports of 21 (5) and 150 (6) patients with MBC comprised of unusually high proportions of patients with KS provided further support for an association. These studies have been widely quoted, particularly as one of them postulated that the incidence of breast cancer in KS patients may approximate that found among women (5).

A number of additional case reports described concomitant occurrences of MBC and KS. Scheike and others (7) assembled results of five studies that showed 9 chromatin-positive males among 242 patients with MBC, or a 3% prevalence rate. Evans and Crichlow (8) comprehensively reviewed 27 reported cases of MBC among KS patients and noted an average age of 58 years, with a high proportion of the cases (13 out of 27) diagnosed with gynecomastia. Based on expected incidence rates in the general population, Scheike and others (7) estimated that KS patients have a 20-fold higher risk of developing MBC than karyotypically normal men and a risk one fifth lower than that of women in the general population. However, even with the higher rates than the general population, KS is generally rare, accounting for only a small proportion of all breast cancers in men. Thus, in the United Kingdom, it has been estimated that the population attributable risk (or the amount of disease attributable to the syndrome) is only 3.6 percent (6).

Differing accounts of the relative occurrence of MBC among KS patients may reflect that reported cases have not been obtained by systematic screening of a defined population with and without the syndrome. One Swedish study attempted to overcome this by systematically karyotyping 93 unselected MBC patients. This found a 7.5% prevalence rate of KS (9), a rate considerably higher than the 3% previously reported rate. These authors estimated that patients with KS have a 50-fold increased risk of developing MBC.

A final complication that affects case reports (as well as epidemiologic studies) is that KS patients may receive greater scrutiny for cancer, i.e., results may be affected by surveillance bias. This could have particular implications for the detection of MBC, a cancer that is often not suspected or given serious diagnostic attention..

Review of Epidemiologic Studies

Case-Control Investigations

An early case-control study found that two of 72 MBC cases tested positive for sex chromatin versus none of 69 controls (10). Another study found two KS patients among their 181 MBC patients (11); this lower prevalence rate of KS most likely reflected that this study focused on men who were eligible for care within the Veterans Administration systems of hospitals.

The largest case-control study focused on prior inpatient medical diagnoses among over 4.5 million U.S. veterans (12). Among 642 men diagnosed with primary MBC during the period 1969-1996, KS was noted as a primary diagnosis among only 5 subjects, resulting in a rate ratio of 29.6 (95% confidence intervals 12.3-71.7). The risk was somewhat higher for black (93.3) than white subjects (20.2), but this difference was based on very small numbers (3

and 2 MBCs, respectively). The prevalence of KS in this investigation was considerably lower than the figure of 7.5% previously noted (9), which was attributed to the fact that individuals eligible for Veterans Administration benefits must be medically qualified to enter military service. Although gynecomastia, a condition often associated with KS (3), was also found to be a significant risk predictor in this study, no patients had both diagnoses, obviating concerns that this was the factor responsible for the high rates of MBC observed among the KS patients.

Cohort Investigations

Two cohort studies of KS patients have been reported from Denmark and Scotland. The Danish study included 832 men with KS established from the Danish Cytogenetic Register (2). Among KS patients, 3 cases of breast cancer were observed vs. 0 among 4,022 age-matched controls from the general population. The Scottish study (13) focused on 466 X chromatin positive male patients identified through a register of patients with chromosome abnormalities. Follow-up for mortality identified 2 cases of MBC among patients 55 years of age and older, a rate twice as high as that expected among females in the general population.

The largest investigations have been conducted by Swerdlow and colleagues (1, 14, 15). In the first investigation (14), involving 646 patients with KS diagnosed at three cytogenetic centers in the United Kingdom between 1959-1990, 2 deaths from breast cancer were observed. In fact, these two cases were the same as those previously observed in the Scottish study (13). In Swerdlow's analysis, cancer mortality was compared to expected rates based on national population figures, leading to derivation of standardized mortality ratios (SMRs). A SMR of greater than1.0 indicates a higher than expected occurrence, and these two cases resulted in a SMR of 61.7, with 95% confidence intervals (CIs)--a measure of certainty of the measure--ranging from 7.5-222.7.

In a subsequent study, Swerdlow expanded his cohort to include 3,518 men diagnosed with KS at 27 cytogenetic laboratories in the United Kingdom between 1959-2002 (1). In follow-up of the cohort members, 5 subjects were found to have died with breast cancer (SMR 57.8, 95% CI 18.8-135.0), and 4 to have incident breast cancers. Compared to the general population, this translated into a standardized incidence ratio (SIR) of 19.2 (95% CI 5.2-49.2). Although substantially elevated compared to the general population of men, the standardized mortality ratio was significantly lower than expectation when general population rates for women were employed (SMR=0.3, 95% CI 0.1-0.8).

The majority of the cohort members in this investigation had a 47,XXY (n=3,002) or 47,XXY mosaic (n=320) chromosomal constitution. Of note was that the highest risks of either breast cancer mortality or incidence were found among the relatively small group of men with 47,XXY mosaic karyotypes (SMR=222.8, 45.9-651.0, SIR=33.7, 0.9-187.7), the majority of whom (n=226) had a 47,XXY/46,XY karyotype (SMR=235.4, 28.5-850.4).

Biologic Plausibility of Association

In deciphering why KS patients experience high rates of MBC, attention has focused on various biologic and clinical correlates of the condition, including altered hormone levels, administration of exogenous androgens, frequent long-standing gynecomastia, and genetic constitution.

Altered endogenous hormones have been the primary focus for explaining the observed increases in MBC among KS patients. During puberty, KS patients begin to exhibit elevated levels of gonadotrophins and decreased levels of testosterone, resulting in their characteristic body proportions and gynecomastia (16). In adults, low testosterone in relation to estradiol levels are cardinal features of KS, resulting in increased estrogen-to-testosterone ratios (17).

Several well established risk factors for female breast cancer appear to operate through hormonal mechanisms, namely obesity and physical inactivity, and both factors presumably affect MBC risk (18). Obesity has also been frequently associated with KS (19), although in at least one study the increased risk of MBC associated with KS persisted after adjustment for diagnoses of obesity (12). In women, it is generally thought that these factors reflect increased estrogen levels, but in men the underlying mechanisms relate not only to increased estrogens but also to decreased testosterone and sex hormone-binding globulin levels (20). This has led to speculation that alterations in the ratio of estradiol/testosterone might be more relevant for male than female breast cancers, consistent with the hormonal alterations found among KS patients. An altered estrogen/androgen ratio has also been offered as an explanation for a recently observed relationship between bone fractures and an increased risk of MBC (18), given that both hormones appear to be involved with bone maintenance and osteoporosis among men and that androgens tend to decrease preferentially with age. This hypothesis would also be consistent with the fact that KS patients have a predilection for bone loss and fractures (21).

In addition to a focus on altered endogenous hormones, there has been interest regarding possible iatrogenic effects of exogenous hormones. Many KS patients with hypogonadism are treated with androgens, and there are case reports of breast cancer developing after such therapy. One study of 45 KS patients treated with testosterone noted the development of two cases of MBC, both occurring 10 or more years after initiation of therapy (22). Among KS patients, androgen supplementation could still be consistent with an effect of a high estrogen to androgen ratio given that KS patients presumably experience more peripheral conversion of testosterone to estradiol than karyotypically normal men (23).

Another explanation for the increased risk of MBC among KS patients is that many, although far from all, KS patients have gynecomastia, a recognized risk factor for MBC. Despite gynecomastia providing increased tissue at risk, its etiologic relevance to MBC has been questioned. It is possible that surveillance issues or uncontrolled confounding by more direct predictors, such as obesity and correlated hormonal alterations, may be involved. However, it is of note that many KS patients begin to experience gynecomastia early in life and therefore have long-standing conditions. Histologic evidence of a transition from atypical proliferative ductal epithelium in gynecomastia to carcinoma in KS patients has

been reported, supporting the notion of abnormal hormonal stimulation of cell proliferation in the mammary ductal epithelium (24). Further, elevated levels of estrogen and progesterone tissue receptors have been found among KS patients with gynecomastia as compared to other gynecomastia patients (25).

Finally, in addition to the role of endogenous hormones and gynecomastia as predictors of MBC among KS patients, consideration must be given to the possibility that KS patients have a genetic predisposition to MBC. Some studies suggest that the additional X chromosome present in KS is responsible (26, 27). Lynch and others (26) have suggested that XXY males may inherit the same predisposition to breast cancer as XX females. This could affect not only breast cancer, but also other cancers that have been suggested to be elevated among KS patients, including non-Hodgkin lymphomas as well as germ cell mediastinal, lung and intracranial tumors (1). The genetic mechanisms involved with this predisposition are currently unknown, but it is of interest that fibroblasts from 47,XXY patients have been shown to have an abnormally high transformation frequency by simian virus 40 (28), raising the possibility that KS patients share phenomena observed in tumor-susceptible individuals.

Conclusions

Based on the rather scant data available, it can be concluded that KS patients are at an increased risk of developing breast cancer. The most convincing data seem to support that this risk may be around 20-30-fold higher than expected. This risk, although elevated, is still considerably lower than that of women in the general population.

The level of absolute risk of MBC among KS patient does not justify prophylactic mastectomy, but does support the need for patient education, monthly breast self-examinations and periodic physical examination. Although mammography has been shown to be useful in the diagnosis of MBC (29), it is difficult at the moment to determine whether this should be employed among KS patients. There is clearly a need for additional studies to further understand the magnitude of risk of breast cancer among KS patients and to determine whether there are certain factors that might most strongly predict risk. Further studies should allow a better understanding of the biologic mechanisms involved in the genesis of breast cancer among KS patients, enabling future targeted interventions and improved treatment approaches.

Abbreviations

CI	Confidence interval
FSH	Follicle stimulating hormone
KS	Klinefelter syndrome
MBC	Male breast cancer
SIR	Standardized incidence ratio
SMR	Standardized mortality ratio

Reference List

1. Swerdlow AJ, Schoemaker MJ, Higgins CD, Wright AF, Jacobs PA. Cancer incidence and mortality in men with Klinefelter syndrome: a cohort study. J Natl Cancer Inst. 2005; 97:1204–10. [PubMed: 16106025]
2. Bojesen A, Juul S, Birkebaek NH, Gravholt CH. Morbidity in Klinefelter syndrome: a Danish register study based on hospital discharge diagnoses. J Clin Endocrinol Metab. 2006; 91:1254–60. [PubMed: 16394093]
3. Weiss JR, Moysich KB, Swede H. Epidemiology of male breast cancer. Cancer Epidemiol Biomarkers Prev. 2005; 14:20–6. [PubMed: 15668471]
4. Bauer DD, Erickson RL. Male breast cancer; Klinefelter syndrome with prostatic, adrenal and mammary tumors. Northwest Med. 1955; 54:472–6. [PubMed: 14370607]
5. Jackson AW, Muldal S, Ockey CH, O'Connor PJ. Carcinoma of male breast in association with the Klinefelter syndrome. Br Med J. 1965; 1:223–5. [PubMed: 14228155]
6. Harnden DG, Maclean N, Langlands AO. Carcinoma of the breast and Klinefelter's syndrome. J Med Genet. 1971; 8:460–1. [PubMed: 4337761]
7. Scheike O. Male breast cancer. Acta Pathol Microbiol Scand Suppl. Suppl. 1975; 251:3–35. [PubMed: 1138536]
8. Evans DB, Crichlow RW. Carcinoma of the male breast and Klinefelter's syndrome: is there an association? CA Cancer J Clin. 1987; 37:246–51. [PubMed: 3111653]
9. Hultborn R, Hanson C, Kopf I, et al. Prevalence of Klinefelter's syndrome in male breast cancer patients. Anticancer Res. 1997; 17:4293–7. [PubMed: 9494523]
10. Casagrande JT, Hanisch R, Pike MC, et al. A case-control study of male breast cancer. Cancer Res. 1988; 48:1326–30. [PubMed: 3342411]
11. Keller AZ. Demographic, clinical and survivorship characteristics of males with primary cancer of the breast. Am J Epidemiol. 1967; 85:183–99. [PubMed: 6020792]
12. Brinton LA, Carreon JD, Gierach GL, McGlynn KA, Gridley G. Etiologic factors for male breast cancer in the U.S. Veterans Affairs medical care system database. Breast Cancer Res Treat. 2010; 119:185–92. [PubMed: 19330525]
13. Price WH, Clayton JF, Wilson J, Collyer S, De Mey R. Causes of death in X chromatin positive males (Klinefelter's syndrome). J Epidemiol Community Health. 1985; 39:330–6. [PubMed: 4086964]
14. Swerdlow AJ, Hermon C, Jacobs PA, et al. Mortality and cancer incidence in persons with numerical sex chromosome abnormalities: a cohort study. Ann Hum Genet. 2001; 65:177–88. [PubMed: 11427177]
15. Swerdlow AJ, Higgins CD, Schoemaker MJ, Wright AF, Jacobs PA. Mortality in patients with Klinefelter syndrome in Britain: a cohort study. J Clin Endocrinol Metab. 2005; 90:6516–22. [PubMed: 16204366]
16. Paduch DA, Fine RG, Bolyakov A, Kiper J. New concepts in Klinefelter syndrome. Curr Opin Urol. 2008; 18:621–7. [PubMed: 18832949]
17. Wikstrom AM, Dunkel L. Testicular function in Klinefelter syndrome. Horm Res. 2008; 69:317–26. [PubMed: 18504390]
18. Brinton LA, Richesson DA, Gierach GL, et al. Prospective evaluation of risk factors for male breast cancer. J Natl Cancer Inst. 2008; 100:1477–81. [PubMed: 18840816]
19. Bojesen A, Kristensen K, Birkebaek NH, et al. The metabolic syndrome is frequent in Klinefelter's syndrome and is associated with abdominal obesity and hypogonadism. Diabetes Care. 2006; 29:1591–8. [PubMed: 16801584]
20. Wu AH, Whittemore AS, Kolonel LN, et al. Serum androgens and sex hormone-binding globulins in relation to lifestyle factors in older African-American, white, and Asian men in the United States and Canada. Cancer Epidemiol Biomarkers Prev. 1995; 4:735–41. [PubMed: 8672990]
21. Seo JT, Lee JS, Oh TH, Joo KJ. The clinical significance of bone mineral density and testosterone levels in Korean men with non-mosaic Klinefelter's syndrome. BJU Int. 2007; 99:141–6. [PubMed: 17092285]

22. Medras M, Filus A, Jozkow P, Winowski J, Sicinska-Werner T. Breast cancer and long-term hormonal treatment of male hypogonadism. Breast Cancer Res Treat. 2006; 96:263–5. [PubMed: 16418796]
23. Wong FH, Pun KK, Wang C. Loss of bone mass in patients with Klinefelter's syndrome despite sufficient testosterone replacement. Osteoporos Int. 1993; 3:3–7. [PubMed: 8422513]
24. Thomas DB. Breast cancer in men. Epidemiol Rev. 1993; 15:220–31. [PubMed: 8405206]
25. Pensler JM, Silverman BL, Sanghavi J, et al. Estrogen and progesterone receptors in gynecomastia. Plast Reconstr Surg. 2000; 106:1011–3. [PubMed: 11039372]
26. Lynch HT, Kaplan AR, Lynch JF. Klinefelter syndrome and cancer. A family study. JAMA. 1974; 229:809–11. [PubMed: 4367182]
27. Moshakis V, Fordyce MJ, Griffiths JD. Klinefelter's syndrome associated with breast carcinoma and Paget's disease of the nipple. Clin Oncol. 1983; 9:257–61. [PubMed: 6311473]
28. Mukerjee D, Bowen J, Anderson DE. Simian papovavirus 40 transformation of cells from cancer patient with XY-XXY mosaic Klinefelter's syndrome. Cancer Res. 1970; 30:1769–72. [PubMed: 4318704]
29. Mattarella A. Breast cancer in men. Radiol Technol. 2010; 81:361–78M. [PubMed: 20207792]