Cancer Incidence and Mortality in Men with Klinefelter Syndrome: A Cohort Study

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Background: Men with Klinefelter syndrome have one or more extra X chromosomes and have endocrine abnormalities. Case reports have led to suggestions that men with Klinefelter syndrome have elevated risks of several cancers, but published cohort studies have been relatively small. We conducted a nationwide cohort study to examine these risks.

Methods: We followed a cohort of 3518 men who had been cytogenetically diagnosed with Klinefelter syndrome in Britain from 1959 through 2002 and compared their cancer incidence and mortality with that of men in the national population. All statistical tests were two-sided.

Results: The standardized mortality ratio (SMR) for all cancers was 1.2 (95% confidence interval [CI] = 1.0 to 1.4). Compared with the general population, men with Klinefelter syndrome had higher mortality from lung cancer (SMR = 1.5, 95% CI = 1.0 to 2.0), breast cancer (SMR = 57.8, 95% CI = 18.8 to 135.0), and non-Hodgkin lymphoma (SMR = 3.5, 95% CI = 1.6 to 6.6) and lower mortality from prostate cancer (SMR = 0, 95% CI = 0 to 0.7). The standardized mortality ratios were particularly high for breast cancer among men with 47,XXY mosaicism (SMR = 222.8, 95% CI = 45.9 to 651.0) and for non-Hodgkin lymphoma among men with a 48,XXYY constitution (SMR = 36.7, 95% CI = 4.4 to 132.5). The cancer incidence data corroborated these associations.

Conclusions: These results support a hormonal etiology for breast cancer in men and for prostate cancer and suggest that men with Klinefelter syndrome may be at substantially elevated risks for non-Hodgkin lymphoma, breast cancer, and, perhaps, lung cancer. [J Natl Cancer Inst 2005;97:1204–10]

Klinefelter syndrome was first described in 1942 (1), and in 1959, it was discovered that men with Klinefelter syndrome have an excess number of X chromosomes (2). Hypogonadism is characterized by this syndrome, as are various hormonal, physical, and developmental abnormalities (3). Information about the long-term cancer risks among men with Klinefelter syndrome is limited, however, reflecting the lack of large cohort studies. The largest studies to date have been a Danish cohort study of 696 men with Klinefelter syndrome, among whom 39 neoplasms were diagnosed (4), and a British cohort study of 646 men with Klinefelter syndrome, among whom 37 cancer deaths were recorded (5). Although the findings of these two studies were not mutually consistent, when they are considered together with the other literature concerning men with Klinefelter syndrome, primarily case reports, there is substantial evidence that such men have increased risks of breast cancer (6–8) and midline teratoma (4,9,10), and less well-supported suggestions of increased risks of several other malignancies (4,11–14), compared with men in the general population.

To obtain systematic data on cancer incidence and mortality from a larger number of men with Klinefelter syndrome than was included in the previous cohort studies, we gathered information from almost all of the cytogenetics laboratories in Britain about all cases of Klinefelter syndrome diagnosed as far back as records are held, i.e., cases from a population of more than 50 million people over a period of up to 44 years. Here, we report cancer incidence and cancer mortality risks in a follow-up of this cohort.

Subjects and Methods

Study Design and Data Collection

We obtained ethical approval for this study from the Ethics Committee of the London School of Hygiene and Tropical Medicine and other appropriate local and national ethics committees in Britain. At each of the 27 cytogenetics laboratories in Britain (except for two small ones), we extracted identification and diagnostic data on all patients with Klinefelter syndrome with at least three sex chromosomes, diagnosed as far back as records have been kept. We did not include data for the comparatively small number of men whose records indicated that they had 46,XX Klinefelter syndrome because of the potential that such a diagnostic entry could be due to an error in recording or transcribing data for a normal male or female. We excluded from the study all individuals whose cytogenetics laboratory records indicated that they had been karyotyped because of the presence of cancer. Identification data for cohort members were sent to the National Health Service Central Registers for England and Wales and for Scotland. These registers hold records for all National Health Service patients in the respective countries and, therefore, for practical purposes act as virtually complete population registers. Deaths, other exits from follow-up, and, since 1971, cancer registrations are recorded in the registers; hence, by flagging the cohort members in the registers, we were able to obtain information on deaths, emigrations, other losses to follow-up, and cancer incidence in the cohort. The underlying cause of death on death certificates was coded according to the International Classification of Diseases (ICD) revision that was in force in Britain at the time of death, i.e., ICD7 (15) for deaths occurring from 1959 to 1967, ICD8 (16) for deaths occurring from 1968 to 1978, ICD9 (17) for deaths occurring from 1979 to 1999 in Scotland and from

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See “Notes” following “References.”

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Statistical Analysis

To analyze mortality risks, we calculated person-years of follow-up for each cohort member by 5-year age group, calendar year, and country (categorized as England and Wales versus Scotland), beginning on the date of cytogenetic diagnosis and ending on June 30, 2003, or the individual’s date of death, emigration, or other loss to follow-up or 85th birthday, whichever occurred first. Follow-up was censored at age 85 because beyond that age, certification of cause of death is likely to be inaccurate and the national (i.e., expected) mortality rates by 5-year age group are not available. Expected cause-specific mortality in the cohort was calculated by multiplying the age-, calendar year-, and country-specific person-years at risk in the cohort by the corresponding national mortality rates for men. We also calculated expected mortality from breast cancer based on the national rates for women. We “bridge-coded” (i.e., matched the equivalence of codes) between ICD revisions to produce the ICD9 categories shown in the tables. For two cancers, liver cancer and acute myeloid leukemia, it was not possible to bridge-code in a way that included ICD7 and therefore, person-years and deaths in the years in which ICD7 was in force (1959–1967) were omitted from the analysis. We calculated standardized mortality ratios (SMRs), i.e., the ratio of the observed to the expected number of deaths, with 95% confidence intervals (CIs) calculated by assuming a Poisson distribution \( (19) \). We tested the statistical significance of the difference between two SMRs by using an exact method as previously described \( (19) \). We used the Kaplan–Meier method \( (20) \) to calculate cumulative risks. All tests of statistical significance were two-sided and were performed using Stata Statistical Software (version 8.0; Stata Corporation, College Station, TX).

We analyzed cancer incidence in the same way that we analyzed mortality, with the following exceptions: follow-up began on January 1, 1971, or the date of diagnosis, whichever was later, because cancer incidence data were available only from 1971 onward; the first year after cytogenetic diagnosis was censored from the analysis; unless subjects were already censored for the other reasons listed for mortality, follow-up was censored on December 30, 2000, for subjects in England and Wales and on December 31, 1998, for subjects in Scotland because national cancer registration was reasonably complete only until those dates; ICD10 coding for cancer incidence started in 1995 in England and Wales and in 1997 in Scotland; and nonmelanoma skin cancer incidence was excluded because registration of it was incomplete \( (21) \).

RESULTS

A total of 4806 patients with Klinefelter syndrome were recorded at the 25 cytogenetics laboratories included in this study. The first cases of Klinefelter syndrome were diagnosed in 1959 (the first cases of this syndrome cytogenetically diagnosed worldwide), but at most laboratories in the study, the earliest cases were from the 1960s or early 1970s, depending on when the laboratory was founded and how far back their records had been preserved. Sixteen subjects were excluded from the study because cytogenetic testing was a consequence of a cancer diagnosis, 24 subjects were excluded because the year of cytogenetic testing was unknown, and two subjects were excluded because the cytogenetic testing had been conducted in men who were older than 85 years. A further 1224 subjects were excluded because of insufficient information for flagging (largely, the lack of their exact date of birth), and 22 subjects were excluded for other reasons. The latter group included men who had mosaicism with a trisomy \( (i.e., Down syndrome)\), which we excluded, as has been done in a previous study \( (4) \), because of the known association between Down syndrome and cancer risk. The remaining 3518 men were flagged successfully and formed the study cohort. Most of these men had a \( 47,XY \) \( (n \equiv 3002) \) or \( 47,XY \) mosaic \( (n \equiv 320) \) chromosomal constitution, but there were also 146 men with four sex chromosomes and 49 men with five sex chromosomes (Table 1). Of the 320 men with \( 47,XY \) mosaicism, 226 were mosaic with \( 46,XY \), 22 were mosaic with \( 46,XX \), and the remaining 72 were mosaic with other karyotypes. A total of 2171 men (62%) had been diagnosed with Klinefelter syndrome at ages 15–44 years, 757 men (22%) had been diagnosed before the age of 15 years, and 590 men (17%) had been diagnosed when they were older than 44 years.

During follow-up, 461 cohort members died, 18 were censored from follow-up at age 85 years, 17 emigrated, and 52 (1%) were lost to follow-up in other ways, leaving 2970 cohort members who were followed alive to the end of the study period. Total follow-up for the mortality analyses was 52987 person-years, or an average of 15.1 years per person; the longest follow-up was 44 years.

In this cohort, the standardized mortality ratio for death from all causes was 1.5 (95% CI = 1.4 to 1.7), and mortality from cancer overall was non-statistically significantly increased compared with the general population (SMR = 1.2, 95% CI = 1.0 to 1.4) (Table 2). Mortality from lung cancer (SMR = 1.5, 95% CI = 1.0 to 2.0), breast cancer (SMR = 57.8, 95% CI = 18.8 to 135.0), and non-Hodgkin lymphoma (SMR = 3.5, 95% CI = 1.6 to 6.6) were all statistically significantly increased, and mortality from prostate cancer was statistically significantly decreased.

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### Table 1. Characteristics of the cohort

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of patients</th>
<th>Person-years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Karyotype</td>
<td></td>
<td></td>
</tr>
<tr>
<td>47,XXY</td>
<td>3002</td>
<td>45233</td>
</tr>
<tr>
<td>47,XXY mosaic</td>
<td>320</td>
<td>4399</td>
</tr>
<tr>
<td>48,XXY</td>
<td>55</td>
<td>972</td>
</tr>
<tr>
<td>48,XXYY</td>
<td>80</td>
<td>1328</td>
</tr>
<tr>
<td>49,XXXXY</td>
<td>48</td>
<td>860</td>
</tr>
<tr>
<td>4 or 5 sex chromosomes, mosaic</td>
<td>12</td>
<td>168</td>
</tr>
<tr>
<td>Klinefelter unspecified</td>
<td>1</td>
<td>27</td>
</tr>
</tbody>
</table>

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1979 to 2000 in England and Wales, and ICD10 \( (18) \) for deaths occurring from 2000 to 2003 in Scotland and from 2001 to 2003 in England and Wales.
Hodgkin lymphoma among men with a 48,XXYY chromosome constitution was 36.7 (95% CI = 4.4 to 132.5). The standardized mortality ratio for non-Hodgkin lymphoma was 32.6 (95% CI = 6.7 to 95.4), based on three cases (data not shown).

Although no mediastinal or pineal tumors were recorded, there was a statistically significantly increased risk of prostate cancer. An analysis of cancer mortality, revealed that men who had more than three sex chromosomes had a particularly elevated incidence of prostate cancer (SMR  =  50.0, 95% CI  =  17.6 to 121.1; P<.001) and the standardized incidence ratio (SIR) was 21.3 (95% CI  =  4.4 to 62.3; P<.001).

The cancer incidence analyses included 39,574 person-years of follow-up. A total of 95 cancers other than nonmelanoma skin cancer were diagnosed 1 year or longer after cytogenetic diagnosis. The overall incidence of cancer was not elevated in this cohort, but there was a statistically significantly elevated incidence of breast cancer and non-statistically significantly elevated incidences of non-Hodgkin lymphoma and lung cancer (Table 4).

The cumulative risks of occurrence of breast cancer, non-Hodgkin lymphoma, and lung cancer by age 75 years were 0.9% (95% CI  =  0.3 to 3.1), 1.9% (95% CI  =  0.9 to 4.1), and 9.2% (95% CI  =  6.3 to 13.3), respectively. The relative risk of gallbladder cancer was 2.4 (95% CI  =  0.1 to 13.5), based on only one case. There was a statistically significantly decreased risk of prostate cancer.

For 15 of the 33 lung cancer cases, tumor histology was coded only as malignant neoplasm (five cancers) or carcinoma (10 cancers); the remaining lung cancer cases comprised eight small-cell cancers, one large-cell cancer, four squamous cell cancers, one anaplastic cancer, and four adenocarcinomas. An analysis of cancer incidence by karyotype, using the same karyotype categories used in the analysis of cancer mortality, revealed that men who had more than three sex chromosomes had a particularly elevated incidence of non-Hodgkin lymphoma (SIR  =  16.2, 95% CI  =  3.3 to 47.4), but there was no clear indication that men with different karyotypes had different incidences of breast or lung cancer (Table 3).

Table 2. Cancer mortality in patients with Klinefelter syndrome by selected cancer site or type*

<table>
<thead>
<tr>
<th>ICD9 code</th>
<th>Cancer site or type</th>
<th>No. of deaths</th>
<th>SMR (95% CI)</th>
<th>P†</th>
<th>AER</th>
</tr>
</thead>
<tbody>
<tr>
<td>150</td>
<td>Esophagus</td>
<td>5</td>
<td>1.2 (0.4 to 2.7)</td>
<td>.84</td>
<td>1.4</td>
</tr>
<tr>
<td>151</td>
<td>Stomach</td>
<td>4</td>
<td>0.7 (0.2 to 1.9)</td>
<td>.73</td>
<td>-2.8</td>
</tr>
<tr>
<td>153-154</td>
<td>Colon and rectum</td>
<td>5</td>
<td>0.6 (0.2 to 1.3)</td>
<td>.23</td>
<td>-7.5</td>
</tr>
<tr>
<td>156</td>
<td>Gallbladder</td>
<td>1</td>
<td>3.3 (0.1 to 18.3)</td>
<td>.53</td>
<td>1.3</td>
</tr>
<tr>
<td>157</td>
<td>Pancreas</td>
<td>4</td>
<td>1.1 (0.3 to 2.9)</td>
<td>.93</td>
<td>0.9</td>
</tr>
<tr>
<td>162</td>
<td>Lung</td>
<td>40</td>
<td>1.5 (1.0 to 2.0)</td>
<td>.03</td>
<td>23.7</td>
</tr>
<tr>
<td>164.2-164.9</td>
<td>Mediastimum</td>
<td>0</td>
<td>0 (0 to 84.5)</td>
<td>1.00</td>
<td>-0.1</td>
</tr>
<tr>
<td>172</td>
<td>Melanoma</td>
<td>2</td>
<td>2.0 (0.2 to 7.2)</td>
<td>.53</td>
<td>1.9</td>
</tr>
<tr>
<td>174-175</td>
<td>Breast</td>
<td>5</td>
<td>57.8 (18.8 to 135.0)</td>
<td>&lt;.001</td>
<td>9.3</td>
</tr>
<tr>
<td>185</td>
<td>Prostate</td>
<td>0</td>
<td>0 (0 to 0.7)</td>
<td>.008</td>
<td>-10.3</td>
</tr>
<tr>
<td>186</td>
<td>Testis</td>
<td>0</td>
<td>0 (0 to 11.4)</td>
<td>1.00</td>
<td>-0.6</td>
</tr>
<tr>
<td>188</td>
<td>Bladder</td>
<td>0</td>
<td>0 (0 to 1.3)</td>
<td>.12</td>
<td>-5.3</td>
</tr>
<tr>
<td>191-192</td>
<td>Nervous system</td>
<td>4</td>
<td>1.2 (0.3 to 3.1)</td>
<td>.84</td>
<td>1.3</td>
</tr>
<tr>
<td>193</td>
<td>Thyroid</td>
<td>1</td>
<td>7.5 (0.2 to 41.9)</td>
<td>.25</td>
<td>1.6</td>
</tr>
<tr>
<td>196-199</td>
<td>Primary site unknown</td>
<td>7</td>
<td>1.2 (0.5 to 2.4)</td>
<td>.78</td>
<td>2.0</td>
</tr>
<tr>
<td>201</td>
<td>Hodgkin disease</td>
<td>0</td>
<td>0 (0 to 7.9)</td>
<td>1.00</td>
<td>-0.9</td>
</tr>
<tr>
<td>200, 202</td>
<td>Non-Hodgkin lymphoma</td>
<td>9</td>
<td>3.5 (1.6 to 6.6)</td>
<td>.003</td>
<td>12.1</td>
</tr>
<tr>
<td>203</td>
<td>Myeloma</td>
<td>1</td>
<td>0.9 (0.02 to 5.0)</td>
<td>1.00</td>
<td>-0.2</td>
</tr>
<tr>
<td>204-8</td>
<td>Leukemia</td>
<td>4</td>
<td>1.7 (0.5 to 4.3)</td>
<td>.43</td>
<td>3.1</td>
</tr>
<tr>
<td>205.0</td>
<td>Acute myeloid leukemia</td>
<td>2</td>
<td>2.0 (0.2 to 7.2)</td>
<td>.53</td>
<td>1.9</td>
</tr>
<tr>
<td>140-208</td>
<td>All malignancies</td>
<td>99</td>
<td>1.2 (1.0 to 1.4)</td>
<td>.13</td>
<td>27.7</td>
</tr>
</tbody>
</table>

*ICD9 = International Classification of Diseases, ninth revision (17); SMR = standardized mortality ratio; CI = confidence interval; AER = absolute excess risk per 100,000 person-years.

†Two-sided, exact method.

(SMR = 0, 95% CI = 0 to 0.7), compared with the general population (Table 2). Autoimmune disease was not mentioned on any of the death certificates for men whose cause of death was non-Hodgkin lymphoma. When we recalculated the breast cancer risk using expected rates for women, the standardized mortality ratio for breast cancer was 0.3 (95% CI = 0.1 to 0.8). There were no deaths from mediastinal or pineal tumors, two malignancies that have been noted previously in patients with Klinefelter syndrome (4,9,10,12).

We also examined cancer mortality among Klinefelter syndrome subjects with different karyotypes (Table 3) and found that men who had a 47,XXY mosaic karyotype had a somewhat greater standardized mortality ratio for cancer overall than men who had a 47,XXY karyotype, primarily because of their greater standardized mortality ratios for lung cancer and breast cancer. Among men who had a 47,XXY mosaic karyotype, seven of the eight lung cancer deaths were in men with a 47,XXY/46,XY chromosome constitution (SMR = 2.5, 95% CI = 1.0 to 5.1; P = .049), and the three breast cancer deaths were in men whose chromosome constitution was 47,XXY/46,XY (SMR = 235.4, 95% CI = 28.5 to 850.4; P<.001) or 47,XXY/46,XX (SMR = 960.4, 95% CI = 24.3 to 5351; P=.002) (data not shown). Only two cancer deaths occurred among patients who had more than three sex chromosomes; both deaths were from non-Hodgkin lymphoma (SMR = 18.8, 95% CI = 2.3 to 67.9). The standardized mortality ratio for non-Hodgkin lymphoma among men with a 48,XXYY chromosome constitution was 36.7 (95% CI = 4.4 to 132.5).

We repeated all of the above analyses after excluding events and person-years during the first year of follow-up and, separately, after excluding events and person-years during the first 3 years of follow-up. None of the results changed appreciably. In particular, mortality from breast cancer and non-Hodgkin lymphoma was statistically significantly increased, mortality from prostate cancer was statistically significantly decreased, and mortality from lung cancer was non-statistically significantly increased compared with the general population (data not shown). Similarly, analyses that excluded the cases from the MRC Human Genetics Unit register (the only research register in the study; all other sources of cases were routine clinical units) did not materially alter the results; for breast cancer, the standardized mortality ratio was 55.1 (95% CI = 11.4 to 161.1; P<.001) and the standardized incidence ratio (SIR) was 21.3 (95% CI = 4.4 to 62.3; P<.001). The cancer incidence analyses included 39,574 person-years of follow-up. A total of 95 cancers other than nonmelanoma skin cancer were diagnosed 1 year or longer after cytogenetic diagnosis. The overall incidence of cancer was not elevated in this cohort, but there was a statistically significantly elevated incidence of breast cancer and non-statistically significantly elevated incidences of non-Hodgkin lymphoma and lung cancer (Table 4).
We also conducted analyses by attained age (data not shown). For cancer overall, there was a slight indication that relative risks of cancer mortality, but not of cancer incidence, decreased with increasing age (SMRs of 1.4 [95% CI = 0.6 to 2.7], 1.4 [95% CI = 1.0 to 1.8], and 1.0 [95% CI = 0.7 to 1.3]) and SIRs of 1.0 [95% CI = 0.5 to 1.7], 1.0 [95% CI = 0.7 to 1.4], and 0.8 [95% CI = 0.6 to 1.1]) for men younger than 45 years, men 45–64 years, and men 65 years or older, respectively). However, there was no clear gradient of relative risk with age for any individual cancer site, including lung cancer, breast cancer, and non-Hodgkin lymphoma.

**DISCUSSION**

In this study, which was based on larger numbers than previous cohort studies, we found that men with Klinefelter syndrome had statistically significantly elevated incidences of and mortality from certain malignancies. Despite the methodology strengths of the cohort design of our study, especially compared with the case reports on which much of the literature has been based, there are several possible limitations that should be considered.
Potential selection of the patients included in this cohort and in previous cohorts could have led to bias. These studies, of necessity, included only men with Klinefelter syndrome who had reached cytogenetic diagnosis. Given that the prevalence of Klinefelter syndrome at birth is at least 1 in 1000 male births (22,23) and that there are about 350,000–400,000 male births per year in Britain, one would expect at least 350 boys with the syndrome to be born each year. However, on the basis of the cases we identified at the cytogenetics centers, our data suggest that, at most, approximately 100 cases of Klinefelter syndrome per year of birth were diagnosed in Britain, i.e., that only a minority of cases reached cytogenetic diagnosis. In recent decades, this selection will essentially have been with regard to which cases were diagnosed clinically rather than whether cytogenetic examination was undertaken for clinically diagnosed cases—virtually all clinically diagnosed cases should have received cytogenetic confirmation, because such diagnosis is free under the National Health Service.

In general, the factors that lead to a clinical diagnosis of Klinefelter syndrome (e.g., the degree of phenotypic abnormality) do not give obvious potential for bias in subsequent risks of cancer, and indeed, from the perspective of patient counseling, the risks of cancer in diagnosed cases of Klinefelter syndrome are the clinically relevant ones. One exception, however, involves the diagnosis of leukemia, which frequently includes cytogenetic examination of the marrow; Klinefelter syndrome may be diagnosed because of a leukemia diagnosis, with potential bias. However, other cancer diagnoses might lead to a clinical suspicion of Klinefelter syndrome, albeit less directly, and hence to a karyotype analysis. Our cancer incidence analyses avoided potential bias from this mechanism because cancer risks were analyzed only for the period more than 1 year after karyotyping [unlike the Danish cohort study (4), which included in the analysis cancers diagnosed before the diagnosis of Klinefelter syndrome]. For cancer mortality analyses, however, bias could potentially occur because deaths that occurred after karyotyping could be due to cancers that were incident before it. To prevent such bias, we excluded from the cohort subjects whose cytogenetic abnormality was recorded as diagnosed because of the occurrence of cancer. The similar mortality results with and without exclusion of the early years after cytogenetic diagnosis suggest that this exclusion was successful and that there was no material bias (which would increase early mortality) in the results.

We could include in the cohort only men who had been diagnosed with Klinefelter syndrome in years for which the cytogenetic laboratories had retained their records (although, in general, this period was as long as the laboratory had been in existence) and men for whom the date of birth had been recorded. Neither restriction, however, could plausibly relate to future risk of cancer.

Cancer registration in Britain has been only approximately 90% complete (21), which, in principle, should not cause bias because it applies to both the observed and the expected numbers of cancers in the analyses. There is a further few percent incompleteness in National Health Service Central Register reporting of registered cancers to study investigators (21), however, which would bias standardized incidence ratios slightly downward. It accorded with this that for the key raised risks (breast cancer, lung cancer, and non-Hodgkin lymphoma), the standardized incidence ratios corroborated, but were slightly lower than, the standardized mortality ratios.

The only generally accepted risk factor for Klinefelter syndrome is older maternal age (24), which is not a known risk factor for any of the cancers for which statistically significant results were found in the cohort. Differences in lifestyle between patients with Klinefelter syndrome and the general population could, in principle, confound examination of (or be intermediate in) an association between a Klinefelter syndrome genotype and cancer risk. Klinefelter syndrome patients with an XXY karyotype have an average IQ that is approximately 10 points lower than that of the general population, and those with four or more sex chromosomes have a much lower IQ (3). However, it seems implausible that, with the possible exception of the lung cancer risk, discussed below, the lifestyles of patients with Klinefelter syndrome associated with their intelligence level could explain the statistically significant results.

The evidence that patients with Klinefelter syndrome have an elevated risk of breast cancer comes largely from studies that karyotyped men with breast cancer (7,8); however, those studies, although they clearly show an elevated risk, were methodologically unsatisfactory to quantify this risk. The only other cohort study independent of the present one that examined cancer incidence found no cases of breast cancer among men with Klinefelter syndrome (4), but given that only 0.05 cases were expected, the (unpublished) 95% confidence interval for the risk estimate must have been wide. The U.K. cohort study published by Price et al. (25) included two deaths from breast cancer, and a subsequent analysis extending the same cohort included the same two cases (5). Our much larger U.K. cohort included seven patients who died of breast cancer and/or had a breast cancer registration during the study analysis period, and risks were statistically significantly increased (P<.001) even if the subcohort giving rise to the two originally reported cases (the MRC Human Genetics Unit subcohort) was excluded.

Men with Klinefelter syndrome have been found to have plasma estradiol levels that are, on average, up to twice those of normal men (26,27). This modest difference makes the magnitude of the breast cancer risk among the men with Klinefelter syndrome (approximately 60-fold higher mortality compared with men in general) somewhat surprising if estrogens were responsible. Possible reasons for the large relative risk are that men with Klinefelter syndrome have an estradiol-to-testosterone ratio that is severalfold higher than that of karyotypically normal men or that there is increased peripheral conversion of testosterone to estradiol in men with Klinefelter syndrome compared with karyotypically normal men (26). Another possibility is that the presence of two X chromosomes per se might increase the genetic risk of breast cancer in men with Klinefelter syndrome (28).

Breast cancer risk was greatest in men with 47,XXY mosaicism, especially those with a 47,XXY/46,XY karyotype. Although we can find no direct data on estrogen levels in individuals with 47,XXY mosaicism, a review of published cases suggests that elevated levels of gonadotrophins (and gynaecostasia) are more common in 47,XXY men than in 47,XXY/46,XY men (29).

We also found that the men in our cohort had an elevated incidence of and mortality from non-Hodgkin lymphoma (only the latter of which was statistically significant), which was not seen in the smaller Danish cohort (4), although the upper confidence limit in the Danish data (4.5) would include our relative risk estimate. There have been several case reports of lymphoma in patients with Klinefelter syndrome (14,30), but these do not provide evidence about risk. The elevated risk of non-Hodgkin lymphoma in our cohort suggests the possibility that immunologic deficiency...
is an etiologic factor for this tumor. To the best of our knowledge, there are no direct data on whether immunologic abnormalities occur in patients with Klinefelter syndrome; however, on the basis of case reports, there are suggestions that the prevalence of autoimmune diseases such as systemic lupus erythematosus may be elevated among men with Klinefelter syndrome (3,31). The risk of non-Hodgkin lymphoma was particularly great in men who had more than three sex chromosomes, a rare karyotype for which cancer risks have not been published in cohorts independent of the present one. Our analysis of risk of non-Hodgkin lymphoma in men with a 48,XXYY chromosome constitution was entirely data driven and needs re-examination in other studies, but very large relative risks that have been based on three cases have often in the past proven to be real (32).

Our data showed a statistically significant deficit of prostate cancer cases among men with Klinefelter syndrome. The smaller Danish cohort (4) had only one case of prostate cancer, with 2.2 cases expected, although that difference was not statistically significant. The deficit we observed adds support to theories about the androgenic etiology of this malignancy (33) because men with Klinefelter syndrome have substantially decreased androgen levels (26,29). Interpretation of the results is complicated, however, because men with Klinefelter syndrome are sometimes treated with testosterone, but it is often not well tolerated and therefore discontinued, and we do not know to what extent the men in this cohort used testosterone.

The risk of testicular cancer in men with Klinefelter syndrome is of interest in relation to theories about testicular cancer etiology generally (34). Men with Klinefelter syndrome typically have testicular atrophy, decreased androgen levels, and elevated gonadotrophin levels. In the Danish cohort (4), one testicular cancer occurred and 1.75 testicular cancers were expected. Analysis of testicular biopsy samples from 35 patients with Klinefelter syndrome found no cases of carcinoma in situ of the testis (35). The absence of raised risk of testicular cancer in our cohort, with a narrower confidence interval than in previous data, argues against the theory that testicular atrophy or raised gonadotrophin levels are etiologically associated with risk of this malignancy.

The association between Klinefelter syndrome and the occurrence of mediastinal germ cell tumors has been shown both by karyotype analysis of a series of patients with such tumors (9) and by follow-up of the Danish cohort (4). All reported cases of mediastinal germ cell tumors have been diagnosed in children or in young men (age 31 years at oldest) (10). No mediastinal germ cell tumors were registered or were the cause of death in our cohort. Although the 95% confidence interval for mediastinal cancer incidence risk in our study included greatly increased risk, it did not encompass the standardized incidence ratio estimated in the Danish cohort (4). The latter study, however, included cancers that were diagnosed before karyotyping and therefore were potentially the reason for karyotyping; if these cases were mediastinal tumors, their inclusion in the analysis could greatly have biased the results toward apparently greater risks. Our study analyzed follow-up only after cytogenetic diagnosis. A substantial proportion of our cohort members (37%) were cytogenetically diagnosed when they were older than 31 years—i.e., older than the presumed ages of high risk for mediastinal teratoma. This age distribution reduced, but did not bias, the amount of relevant follow-up for this tumor. There have been several case reports of pineal teratomas in men with Klinefelter syndrome (12,32); there were no pineal teratomas recorded as such in our cohort, but the one teratoma that was coded as “brain unspecified” could have been pineal.

In the Danish cohort (4), there was a statistically significantly elevated risk of cancer of the gallbladder and extrahepatic bile duct, based on two cases. We found a non-statistically significantly elevated risk of gallbladder cancer, based on only one case, giving slight support to the Danish finding.

Our raised risk for lung cancer was similar to the non-statistically significant result in the Danish cohort (4). We had no information on smoking in our cohort, and although there is no obvious reason why men with Klinefelter syndrome should smoke much more than men in the general population, such a difference is possible. The standardized mortality ratios and standardized incidence ratios for other cancer sites that are strongly associated with smoking (i.e., mouth and pharynx, esophagus, pancreas, larynx, and bladder), however, were near or less than 1.0 in this cohort. The lung cancers in our cohort were diagnosed at ages 43 years and older, whereas all published cases of midline teratoma were diagnosed at ages younger than 32 years; thus, it seems unlikely that the excess of lung cancers was a consequence of misdiagnosed mediastinal tumors. The distribution of histologic types of lung cancer in our cohort, especially the large proportion of small-cell tumors, was somewhat unusual (36), but again, was based on small numbers.

On the basis of case reports (11,14,37), it has been suggested that men with Klinefelter syndrome have an increased risk of leukemia (11). We found a non-statistically significant elevated risk of leukemia in our cohort, leaving open the possibility of a modest association between Klinefelter syndrome and this malignancy. The Danish cohort study (4) did not find an elevated risk, but the confidence interval for the risk estimate was wide. A systematic review of cytogenetic diagnoses among 1200 male leukemia patients in British Columbia did not find a raised prevalence of Klinefelter syndrome (38), although the (unpublished) confidence intervals must have been wide because of small numbers—Klinefelter syndrome would be expected in only about 1 in 1000 men.

In summary, we found statistically significant elevations in risks of breast and lung cancers and non-Hodgkin lymphoma and a statistically significant reduction in risk of prostate cancer in men with Klinefelter syndrome that do not appear to be due to bias or confounding. Endogenous sex hormone levels and putative immunologic mechanisms might explain some of these risk alterations. However, it is also possible that the patients’ genetic constitutions might be directly responsible for their altered cancer risk. For example, the frequency of SV40 transformation of fibroblasts from a cancer patient with mosaic Klinefelter syndrome was 3 to 10 times greater than that in fibroblasts from individuals with normal karyotypes and no history of cancer and was three times greater in the patient’s XXY cells than in his XY cells (39). Elevated risks of non-Hodgkin lymphoma and breast cancer among men with Klinefelter syndrome might also be due to overexpression of an oncogene on the X chromosome that escapes X inactivation. Whatever the mechanism(s) for the elevated cancer incidence, our data indicate several tumors for which clinical suspicion should be high in men who have Klinefelter syndrome.

REFERENCES

1. Klinefelter HG Jr, Reifenstein EC Jr, Albright F. Syndrome characterized by gynecomastia, aspermatogenesis without a-Leydigism and increased


Notes

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