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Prevalence, Incidence, Diagnostic Delay, and Mortality in Turner Syndrome

Kirstine Stochholm, Svend Juul, Knud Juel, Rune Weis Naeraa, and Claus Højbjerg Gravholt

Medical Department M (Endocrinology and Diabetes) (K.S., C.H.G.), Aarhus Sygehus NBG, Aarhus University Hospital, and Department of Epidemiology (S.J.), Institute of Public Health, Aarhus University, DK-8000C Aarhus, Denmark; National Institute of Public Health (K.J.), DK-1399K Copenhagen, Denmark; and Pediatric Department (R.W.N.), Randers Centralsygehus, DK-8900 Randers, Denmark

Aim: Our aim was to study prevalence, incidence, age at diagnosis, and mortality in Turner syndrome (TS) in Denmark.

Methods: Using the Danish Cytogenetic Register, we identified all cases (n = 781) of TS alive in Denmark during 1970–2001. Sixty-nine deceased women with TS were identified in the Causes of Death Register. We divided the cohort into women having the karyotype 45,X, karyotypes including an isochromosome Xq, and all other karyotypes associated with TS. We describe the number of patients diagnosed in Denmark yearly, incidence rates, and the age at diagnosis. Standardized mortality ratios (SMR) were calculated.

Results: A total of 349 women had a 45,X karyotype, 86 had a karyotype including an isochromosome Xq (isoXq), and 346 had another TS karyotype. Mortality was increased in TS with an SMR of 2.86 (95% confidence interval, 2.18–3.55). SMR was increased for coronary diseases, congenital malformations, endocrine diseases, and other causes. The mortality was increased for all types of karyotypes in comparison with the general population but was highest among females with 45,X and isoXq. There was a steady increase in prevalence, but incidence was unchanged. Age at diagnosis was mainly distributed in three periods: less than 1 yr of age (14.9%), during adolescence (10–17 yr) (33.2%), and during adulthood (38.5%), with a median age at diagnosis of 15.1 yr, decreasing during the study period ($P < 0.01$).

Conclusions: Patients with TS and especially the karyotypes 45,X and isoXq have a higher mortality compared with the background population. TS was diagnosed with a considerable diagnostic delay. Prevalence is increasing, but incidence of TS was stable. **(*J Clin Endocrinol Metab* 91: 3897–3902, 2006)**

TURNER SYNDROME (TS) is characterized by the absence of part of or the entire X chromosome in a woman, with typical stigmata like short stature, primary amenorrhea, estrogen insufficiency, and cardiovascular malformations. Various karyotypes and phenotypes exist (1). An increased risk of congenital malformations and aortic dissection is seen (2). Increased morbidity is seen, with increased risk of osteoporosis and fractures, type 2 diabetes, ischemic heart disease, hypertension, and stroke (3). An early British report suggested that mortality was also increased (4); however, this study was rather small. In 2001, Swerdlow *et al.* (5) extended the British data and described how mortality in TS is elevated, with an increased risk of death from diseases of the nervous, cardiovascular, respiratory, digestive, and genitourinary systems.

Congenital conditions like TS are present from intrauterine life and onward but may be diagnosed at any point during a lifetime, as opposed to most medical conditions that arise at some point in life and are subsequently diagnosed. Two key epidemiological terms, incidence and prevalence, may therefore easily become confused. In the following, we denote the proportion of a population of females with TS at birth as prevalence at birth (6), and we distinguish between true and known prevalence. We use the term incidence when describing the annual number of cases diagnosed.

We pooled data from a number of cytogenetic studies performed more than 20 yr ago, and based on these studies, we estimated a true prevalence at birth of 50 TS per 100,000 females (pooled population, 48,744 females; pooled TS, 24 females) (7–11). Previously, we found a prevalence of cases diagnosed postnatally of 32 per 100,000 females (12). A considerable delay in diagnosing girls and adolescents with TS was seen in pediatric populations (13, 14), although the delay seems to be diminishing in recent years (14).

To our knowledge, incidence, prevalence, age at diagnosis, and mortality in TS have not been described in an unselected population in a nationwide study. We therefore undertook an investigation among all women with a TS karyotype to study these parameters, including a detailed assessment of all deceased women with TS to identify causes of death.

Patients and Methods

We identified all patients in Denmark diagnosed postnatally with TS in the Danish Central Cytogenetic Register (DCCR) before December 31, 2001. Since 1968 when DCCR was founded, all diagnosed cases of TS in Denmark have been reported from the seven laboratories performing chromosome karyotyping. Data from cases diagnosed before 1968 were also included in the register. The register includes information on karyotype and date of diagnosis and contains approximately 200,000 cytogenetic examinations; of these, 160,000 are prenatal and 40,000 postnatal examinations; the annual number of examinations is approximately 10,000. About 8% of all pregnant women in Denmark were subjected to prenatal analysis during the study period. Some cases of TS are thus diagnosed intrauterine, but few are born because of a high legal abortion

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Abbreviations: CI, Confidence interval; DCCR, Danish Central Cytogenetic Register; HRT, hormone replacement therapy; ICD, International Classification of Diseases; SMR, standardized mortality ratio; TS, Turner syndrome.

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rate of 70–80%, a percentage that has risen through recent years. Only prenatally diagnosed TS cases subsequently verified postnatally are included here, excluding very few prenatally diagnosed cases, not verified postnatally, from the statistical analyses. It is important to stress that the register contains only information regarding karyotype and no information regarding phenotype. Postnatal karyotype examinations are performed based on clinical signs of TS, which differ widely in relation to the age of a given individual (13). Thus, the karyotype of all women with diagnosed TS in Denmark is registered in the DCCR. Part of this cohort has previously been used in a registry study linking DCCR with the National Registry of Patients to describe morbidity (3).

From the Causes of Death Register we obtained a copy of the death certificate for every deceased woman with TS, and from The National Institute of Public Health we obtained the age- and calendar-specific rates for the cause of death divided into 11 International Classification of Diseases (ICD-10) chapters (see Table 2). In the Causes of Death Register, ICD-8 was used from 1969–1993 and ICD-10 from 1994 onward. We translated ICD-8 diagnoses to ICD-10.

For all calculations of mortality, patients entered the study cohort at the date of diagnosis or January 1, 1970, whichever came last. We chose to start the observation period in 1970 to avoid any confounding resulting from a run-in phase in the new DCCR founded in 1968, and we suspect that the mixture of TS females in the early days before systematic registration and karyotyping took place was skewed toward females with a more severe phenotype, possibly introducing an unwanted and hardly controllable bias. Follow-up time ended at the date of death, emigration, or December 31, 1999, whichever came first. All patients were at the latest diagnosed December 31, 1999, and alive at diagnosis. A total of 741 postnatal cases were identified, fulfilling the criterion to contribute time at risk during 1970–1999.

For the calculations regarding prevalence, we focused on 781 cases of TS diagnosed postnatally and alive any time during 1970–2001. For the calculation of incidence, trend in incidence, and median age at diagnosis, we included only patients diagnosed from 1970 onward [n = 704, excluding cases (n = 77) diagnosed before 1970].

The study received approval from the Danish Data Protection Agency and DCCR.

Statistical analysis

Age at diagnosis was studied [median age with 95% confidence intervals (CI) using the binomial distribution), and the differences in median age at diagnosis by karyotype were analyzed using the Kruskal-Wallis test. Time trends in incidence and in median age at diagnosis were analyzed using Poisson and linear regression, respectively. Total and cause-specific standard mortality ratios (SMR) were calculated using 5-yr age groups and 5-yr calendar time periods. The Poisson distribution was used for calculation of exact 95% CI. Kaplan-Meier survival estimates were constructed from age at entry in and age at exit from the cohort. Poisson regression was used to test for differences in mortality among the three groups of females with TS as well as changes in SMR during the study period. $P < 0.05$ was considered significant. Stata 8.2 for Windows (Stata Corp., College Station, TX) was used for all calculations.

Results

Of the grand total of 781 cases, 349 had a karyotype of 45,X, 86 had a karyotype including an isochromosome Xq, and 346 had other TS karyotypes (Table 1). Because of small numbers, we did not subdivide the group of other karyotypes further into karyotype groups containing Y chromosome material or mosaics, such as 45,X/46,XX, which constituted the largest part of this group (n = 120). Preliminary analyses showed that there was no difference between the group 45,X/46,XX and the rest of the subjects in the group of other karyotypes, and we subsequently pooled these two groups in the group of other karyotypes for all other analyses (results not shown).

TABLE 1. Distribution of karyotypes in the study group

Karyotype	N
45,X	349
45,X/46,X,i(Xq); 46,X,i(Xq) or equivalents	86
45,X/46,XX; 45,X/46,X,del(X); 46,X,del(Xp); 45,X/46,X,t(X:X); 46,XXp-; 45,X/46,X,i(Xp); 45,X/46,X,+mar; 45,X/47,XXX	346
Karyotypes containing Y chromosomal material [45,X/46,XY; 45,X/46,X,del(Y)] and others	

Prevalence and incidence

A steady increase in the known number of live TS was observed during the entire study period (Fig. 1). The absolute number of patients diagnosed yearly did not change (Poisson regression $P = 0.39$) during the study period. During 1970–2001, an average of 22 females per year were diagnosed with TS, and approximately 2.6 million women were at risk yearly. Thus, the average incidence rate of TS was 8.5 per million. The cumulated incidence of TS is illustrated in Fig. 2, showing that about 40 TS per 100,000 females have been diagnosed in the cohorts born during 1970–1980, whereas considerably fewer TS females of those born during 1980–2000 have been diagnosed so far.

Age at diagnosis

The median age at diagnosis for the entire TS group was 15.1 yr (95% CI, 14.5–15.8 yr; range, 0–85.4 yr). The age at diagnosis is shown in Fig. 3, and the median age at diagnosis was 13.3 yr (95% CI, 12.1–14.2 yr) for 45,X females, 14.2 yr (12.4–16.2 yr) for females with isoXq, and 19.1 yr (17.8–21.9 yr) for females with any other karyotype. The age at diagnosis was significantly higher in the group of other karyotypes compared with the other two groups (Kruskal-Wallis rank sum $P = 0.0001$). During the study period, we recorded a significant decrease in the median age at diagnosis ($P < 0.01$) (Fig. 4).

Mortality

The overall mortality was increased compared with the general population with an SMR of 2.86 (95% CI, 2.18–3.55)

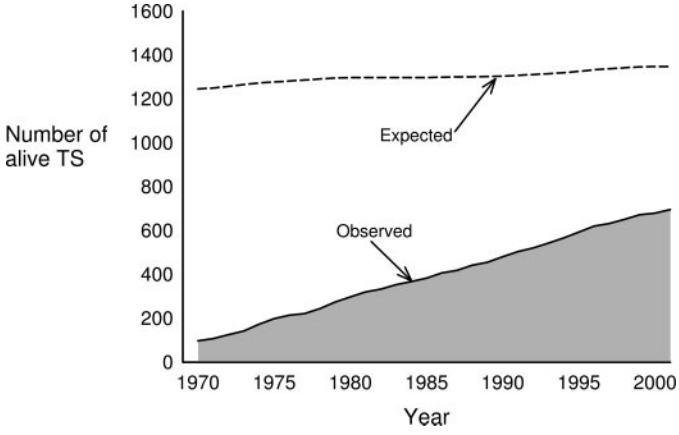

FIG. 1. The absolute number of females with TS during the study period 1970–2001 is illustrated by the *solid line*. Individuals dying or emigrating were subtracted. The *dashed line* indicates the expected number of TS, assuming a true prevalence of 50 TS per 100,000 at birth and similar mortality as in the general population (for details, see *Patients and Methods*).

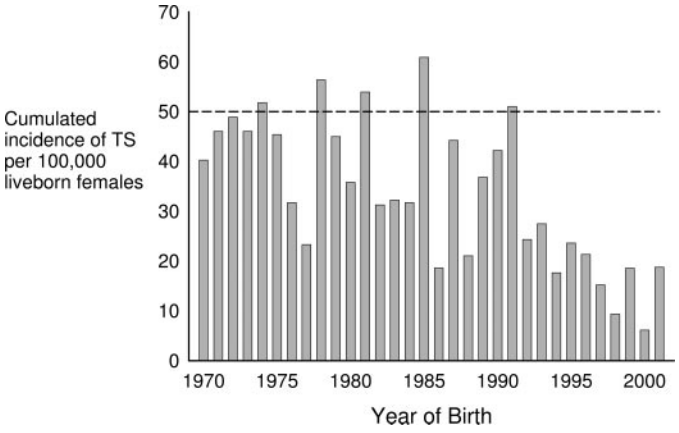

FIG. 2. Cumulated incidence of females with TS born per year during the study period and diagnosed by the end of 2001. The *dashed line* indicates the expected number of TS, assuming a true prevalence of 50 TS per 100,000 at birth and thus corresponding to the expected incidence of TS at birth if all individuals were diagnosed instantaneously. It is obvious from the figure that a number of individuals are awaiting diagnosis.

(Table 2). SMR was significantly increased for all three karyotype groups. Among females with 45,X, SMR was 4.08 (2.79–5.75); among females with isoXq, 3.86 (1.41–8.37); and among other karyotypes, 2.10 (1.42–2.98). Using Poisson regression with the 45,X group as reference group, we found a relative risk of death of 0.94 (95% CI, 0.40–2.26) for females with isoXq, whereas for other karyotypes, the relative risk was significantly decreased at 0.51 (95% CI, 0.31–0.84). Furthermore, we found a tendency toward lower mortality over time although not reaching significance ($P = 0.08$). Mortality in the three groups is illustrated in Fig. 5.

Mortality was significantly increased for endocrine, nutritional, and metabolic diseases, coronary diseases, and congenital anomalies as well as other causes, encompassing a mixed group of accidents, suicide, and unknown reasons (Table 2). Insignificant increases in mortality risk were present for a number of other groups of diseases. We observed a number of different cancers: breast (n = 2), lung (n = 2), colon (n = 2), and urethra, bladder, skin, myeloma, astrocytoma, leukemia, and unknown location (all n = 1). From the individual death certificates, it could be seen that diabetes mellitus was a contributing secondary cause of death in 15 of 69 cases (22%). We observed five cases of dissection of the aorta occurring at the age of 18, 23, 27, 28, and 38 yr.

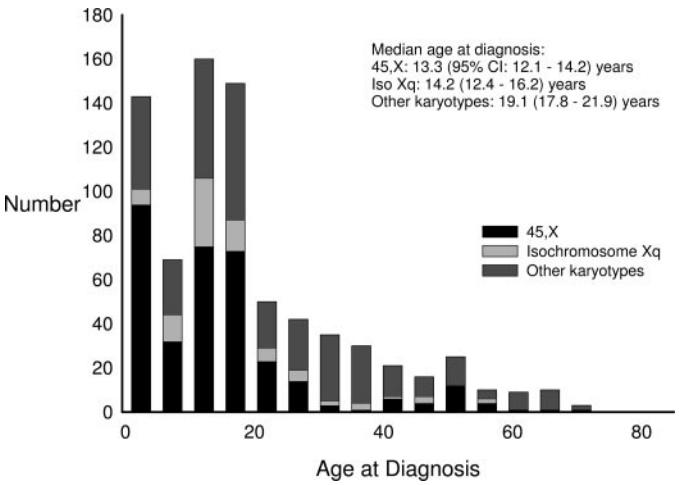

FIG. 3. Age at diagnosis for females with 45,X, an isochromosome Xq, or any other karyotype.

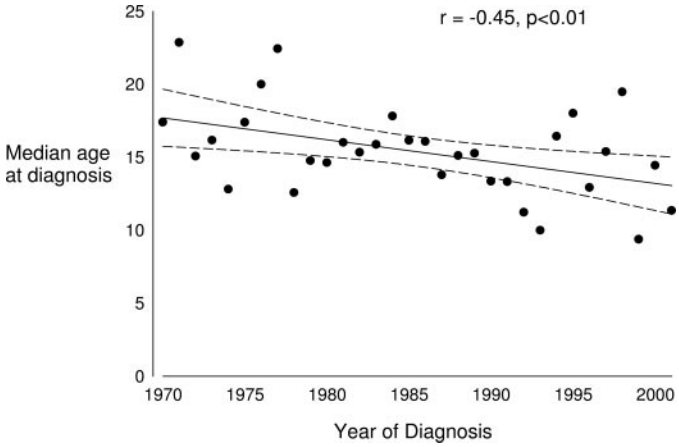

FIG. 4. Age at diagnosis for all TS females during the study period. The *solid line* indicates the regression line, and the *dashed lines* indicate 95% CI. Regression coefficient and significance level are indicated on the graph.

Discussion

Our results show an increased mortality in TS and a considerable delay in diagnosis of the syndrome. The increased mortality is more pronounced than what is seen in another sex chromosome disorder, Klinefelter syndrome (15, 16), but considerably lower than that seen among patients with Down's syndrome (17). The mortality decreased insignificantly during the study period in parallel with a decrease in the population mortality. The recorded prevalence increased during the study period mainly because of the build-up of the register. There was an unchanged incidence during the study period.

We found an overall increased mortality with an SMR of 2.86. Within the group of patients with TS, there were differences, although an increased mortality was present for all chromosomal subgroups. Interestingly, the cause-specific mortality was increased for coronary diseases, congenital malformations, and endocrine, nutritional, and metabolic diseases as well as other causes. However, we could not find an increased risk of dying from pneumonia or other diseases of the respiratory system or of diseases of the digestive and genitourinary systems, as found previously in a smaller group of females with TS (n = 400; deaths, n = 62) in a British study (5). Here, it was also reported that the relative risk of death among TS patients was 4.16 (95% CI, 3.22–5.39). This measure may not be directly comparable with our data, especially because the TS groups studied in Britain and in Denmark differ markedly, the Danish group containing more females with other rarer karyotypes than 45,X known to result in TS, and as a consequence, the fraction of women with the classical karyotype, 45,X, is smaller. We know from previous studies that the fraction of females with TS and karyotypes other than 45,X is increasing in newer studies of TS (12) and that females with karyotypes other than 45,X also suffer from

TABLE 2. Total and cause-specific SMR by main diagnostic groups

	No. of deaths/expected no. of deaths	SMR	95% CI
Infectious and parasitic diseases	1/0.2	4.68	0.12–26.53
Malignant neoplasms	13/7.8	1.67	0.89–2.86
Endocrine, nutritional, and metabolic diseases	3/0.5	5.68	1.17–16.54
Diseases of the nervous system, eye, and ear	2/0.5	4.38	0.53–15.71
Coronary diseases	18/5.2	3.47	2.06–5.48
Cerebrovascular diseases	4/1.8	2.21	0.60–5.66
Congenital anomalies	9/0.4	24.09	11.12–46.18
Diseases of the respiratory system	1/1.5	0.69	0.02–3.82
Diseases of the digestive system	2/1.0	1.96	0.24–7.08
Diseases of the genitourinary system	1/0.3	3.88	0.10–21.43
Other causes	15/5.1	2.95	1.65–4.86
Total	69/24.2	2.86	2.18–3.55
Period[a]			
1970–1979	13/2.8	4.68	2.49–8.00
1980–1989	21/7.34	2.86	1.77–4.37
1990–1999	35/14.05	2.49	1.74–3.46

In addition, total SMR in the different study periods are presented.
[a] Test for trend in mortality during the study period, $P = 0.08$.

increased morbidity (3, 18–21). Discrepancies between our findings and the previous studies could also, in part, be explained by differences in design. We used the same register of causes of death to describe the mortality in both TS and the background population. Data from the Danish Register of Causes of Death are excellent but with a tendency for common causes of death, *e.g.* myocardial infarction, to be overdiagnosed and rare causes, such as cerebral hemorrhage, aortic dissection, and intestinal thrombosis, to be underdiagnosed (22), but we have no reason to believe that the risk of misclassification is different for TS subjects and the background population, and for overall mortality, this is not an issue.

Interestingly, we observed an almost significant decrease in total mortality over the three decades of study. It is not possible to state whether this finding is because of a real decrease in mortality because of better care of individuals with TS or whether it illustrates a change in the composition of the group of TS, with an increased fraction of other karyotypes with time, which we show here to have a lower SMR.

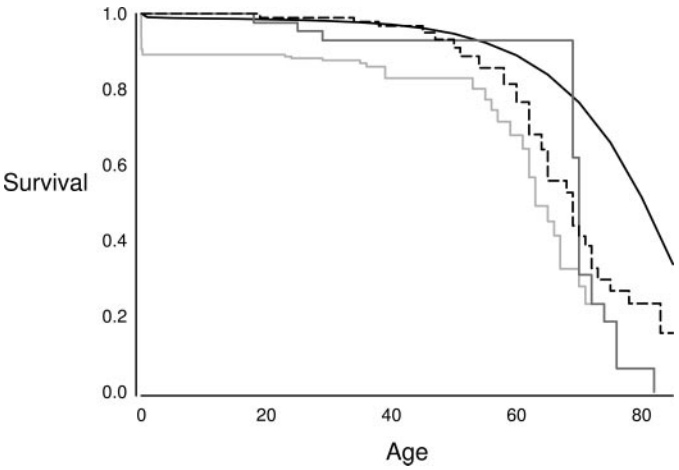

FIG. 5. Kaplan-Meier plots of cumulated mortality in the general population (*black line*), females with 45,X (*light gray line*), females with an isochromosome Xq (*dark gray line*), and females with all other karyotypes associated with TS (*dashed black line*).

The risk of dying from endocrine, nutritional, and metabolic diseases was increased, likely because of an increased frequency of diabetes (3, 20, 23, 24). From studying individual death certificates, it could be seen that diabetes indeed was a frequent contributing cause of death, even in cases where it was not the underlying cause of death. Diabetes may be even more frequent because of possible undiagnosed cases of type 2 diabetes. Thyroid disorders are also frequent in TS (18) but unlikely as underlying causes of death in most cases.

We found a considerably increased risk of congenital anomalies as a cause of death, and although we cannot derive such information from our data, it is likely attributable to malformations of the heart and great arterial vessels. The malformations seen in TS predominantly involve the vessels of the left side of the heart, although venous malformations have also been documented (2, 19, 25–28). Aortic dissection occurs early and with increased frequency in TS (for review, see Ref. 2) and is often accompanied by hypertension, which occurs early in TS (23, 29–31). We recently studied all observed TS cases with aortic dissection in Denmark, including both deceased (included here) and surviving individuals with TS, and estimated that 1.4 in 100 females with TS would suffer from aortic dissection and at a strikingly young age (32). The increased risk of coronary disease may well be explained by the very frequent occurrence of hypertension (~50%) (3, 29, 31, 33); increased carotid intimal thickness, aortic augmentation index, and pulse-wave velocity (34, 35); and lipid abnormalities found by some (36) but not all investigators (23).

Thus, mortality in TS is increased for several reasons, which are potentially amenable to proper treatment. In the present study, we do not know how many were receiving hormone replacement therapy (HRT), but clinically, more than 80% of Danish TS women report the use of HRT (37). Although HRT recently has been nearly abandoned in the postmenopausal setting, there are no data from randomized studies on the impact of HRT on mortality in premenopausal women deprived of endogenous estradiol production. Epidemiological data from female patients in the premeno-

pausal age group with hypopituitarism suggest that treatment with HRT improves survival (38).

The average age at diagnosis of TS of 13, 14, and 19 yr for females with the classical karyotype 45,X, isoXq, or any other karyotype associated with TS is remarkable and surprisingly similar among females with the 45,X and an isochromosome Xq of 13 and 14 yr, whereas individuals with other karyotypes like 45,X/46,XX, deletions of either Xq or Xp, and karyotypes involving a Y chromosome had an even longer median delay of 19 yr. Previously, in a pediatric population, it was shown that the delay to diagnosis was on average 7.7 yr, with a slightly shorter delay of 5.3 yr after an individual had fallen below the fifth percentile for height (13). Likewise, in a Belgian pediatric population, it was found that the median age of diagnosis was 6.6 yr with a wide range of 0–19 yr and improving in comparison with a previous census 12 yr earlier (14). It is not surprising that individuals with karyotypes other than 45,X present longer delays because of the fewer stigmata they typically exhibit; however, studies have also shown unequivocally that women with rarer karyotypes resulting in TS have reduced height and to the same degree as females with 45,X (39–41). Most of these females will also display ovarian failure or very premature ovarian failure (42), and the delay in diagnosis is therefore quite striking; hence the results emphasize the need for increased vigilance of the syndrome among all clinicians. In addition, we estimate that only one tenth of females with TS were diagnosed in 1970, a fraction that had increased to about one half by 2001 (Fig. 1). This information points toward caution when interpreting the present data. But especially interpreting data from older studies, with presumably even more pronounced ascertainment bias, may lead to erroneous conclusions.

The observed increase in prevalence of TS throughout the study period is mainly caused by the build-up of a new registry, with continuing recruitment. Other causes may include a slightly increased diagnostic vigilance among clinicians, leading to a decrease in median age at diagnosis but not to an increase in incidence and perhaps the recorded insignificant decrease in mortality. Changes in the composition of TS karyotypes, with relatively fewer 45,X cases, may also play a role. Our study shows that with a delay of 20–30 yr, most females with clinical symptoms of TS will eventually be diagnosed, anticipating a true prevalence of 50 TS per 100,000 at birth. Of course, our data could also suggest that the true prevalence of TS is even higher and that we do not diagnose all females with TS. The prevalence will of course also be affected by the number of prenatally diagnosed fetuses that are legally aborted. However, because we know that less than 10% of Danish pregnant women have prenatal karyotyping performed, and although a high abortion rate (70–80%) is seen, this figure will only marginally influence the present findings (personal communication with DCCR). This enigma of the true prevalence of TS will be solved only when a complete screening of an entire population is performed. Combining the available data on prevalence, incidence, and diagnostic delay therefore shows that more females with TS are diagnosed today and with a decrease in delay. This decrease in delay to diagnosis may be caused by the contemporary prospects of adequate treatment of reduced height with GH. It is, however, quite clear that new measures need to be taken to diagnose all TS at an early age, and we believe that a karyotype should be included in standard algorithms for the evaluation of short stature.

The limitations of this study are mainly due to lack of clinical data on the subjects. Neither DCCR nor the Causes of Death Register includes any clinical data or data regarding phenotype. The study does not allow determining to what extent the increased mortality among women diagnosed with TS is a direct biological effect of the syndrome *per se* or of hypogonadism and to what extent unfavorable socioeconomic conditions and lifestyle play a role. Furthermore, the cohort of patients is made up of diagnosed cases, and knowing that many females remain undiagnosed, we cannot extend the conclusions of the study to cover such undiagnosed cases.

The strengths of the present study are that this is a nationwide register study, covering all diagnosed TS subjects in Denmark, performed in a uniform public health care system with complete long-term follow-up. By performing standardization for age and calendar time, we were able to adjust for the changing mortality during the decades we were investigating. Furthermore, the study is the largest to date, with the longest study period and 11,030 TS years at risk.

In conclusion, mortality is increased in TS, leading to a considerable decrease in life expectancy. Our data also show a tendency toward a decrease in mortality in TS. Not all individuals with TS are diagnosed, and there is a relatively long diagnostic delay, necessitating more vigilance and knowledge of TS among all clinicians. The prevalence of TS is close to 50 per 100,000 females, but the incidence of TS does not seem to be increasing.

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Address all correspondence and requests for reprints to: Claus Højbjerg Gravholt, M.D., Ph.D., Medical Department M (Endocrinology and Diabetes), Aarhus Sygehus, Nørrebrogade, Aarhus University Hospital, DK-8000 Aarhus C, Denmark. E-mail: ch.gravholt@dadlnet.dk.

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