

Tumour occurrence in women with Turner syndrome: A narrative review and single-centre case series

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Abstract

Background: Population studies suggest cancer morbidity may be different in Turner syndrome (TS) compared to the background female population. However, significant variability is observed in cancer associations likely due to heterogeneity in patient cohorts. We explored the prevalence and patterns of cancer amongst a cohort of women with TS attending a dedicated TS clinic.

Methods: Retrospective analysis of the patient database was performed to identify TS women who developed cancer. Population data (available before 2015) from the National Cancer Registration and Analysis Service database were used for comparison.

Results: Out of 156 TS women, median age of 32 (range 18–73) years, 9 (5.8%) had a recorded cancer diagnosis. Types of cancers were, bilateral gonadoblastoma, type 1 gastric neuroendocrine tumour (NET), appendiceal-NET, gastrointestinal stromal tumour, plasma cell dyscrasia, synovial sarcoma, cervical cancer, medulloblastoma and aplastic anaemia. Median age at cancer diagnosis was 35 (range 7–58) years and two were detected incidentally. Five women had 45,X karyotype, three received growth hormone treatment and all except one received oestrogen replacement therapy. The cancer prevalence of the background age-matched female population was 4.4%.

Conclusions: We confirm the previous observations that women with TS do not appear to be at overall increased risk of common malignancies. Our small cohort showed a spectrum of rare malignancies that are not typically associated with TS, except for a single patient with a gonadoblastoma. The slightly higher prevalence of cancer in our cohort might simply represent increased cancer prevalence in the background population, or might be related to small sample size and regular monitoring of these women due to TS per se.

KEYWORDS

cancer, single-centre study, tumour, turner syndrome

1 | INTRODUCTION

Turner syndrome (TS) is the commonest chromosomal abnormality in females and occurs in approximately 1 in 2500 live female births.¹ It is caused by partial or complete loss of the X chromosome in women and commonly presents with short stature and primary amenorrhoea.

Women with TS have been hypothesized to have an increased risk of cancer when compared to the background female population due to various factors.^{2,3} Intrinsic characteristics of TS, such as haploinsufficiency of X chromosome that might predispose them to develop cancers associated with X chromosome-located microRNA mutations more commonly than females with two X chromosomes such as haematological malignancies,⁴ increased risk of autoimmune diseases could elevate the risk of cancers associated with autoimmunity, for example, lymphoma,⁵ and presence of Y chromosomal material in some women (6%–9% of women with TS would harbour Y chromosome with conventional cytogenetic analysis and up to 4%–38% would harbour cryptic Y chromosome material with advanced molecular analysis) might elevate the risk of developing gonadoblastoma.^{6,7} Additionally, the treatment they receive could theoretically place them at higher risk of developing cancers, such as long-term sex hormone replacement therapy (HRT) that is reported to be associated with breast and uterine cancers in the general female population,⁸ and supraphysiological growth hormone (GH) treatment to enhance height and growth might elevate the cancer risk.⁹

Published evidence of cancer risk in TS (Table 1) shows marked variability in outcomes. TS is a rare syndrome and accumulating a large group of patients to perform high-quality studies is pragmatically difficult. Nevertheless, more recent studies consistently report that the overall cancer risk in TS is not increased when compared to the age-matched female population, whilst the spectrum of reported cancer morbidity is significantly different in this group of patients.^{10–12}

In this context, we set out to explore the prevalence and patterns of cancer amongst a large single-centre cohort of systematically monitored women with TS at a tertiary care centre.

2 | MATERIALS AND METHODS

Data on women with TS, actively followed up in the adult TS clinic of Oxford Centre for Diabetes, Endocrinology and Metabolism (OCDEM) from mid-2015 to end of 2020 were collated. Demographic details and data regarding age at the diagnosis of TS, karyotype, HRT, GH treatment, age at the diagnosis of cancer, tumour type, mode of presentation of malignancy, and other clinically relevant details were collected by retrospective review of paper and electronic patient records. Data were recorded in a password-protected EXCEL spreadsheet on a secure department network. Categorical data were reported as percentage, and frequency and continuous data were reported as median and range.

Twenty-year cancer prevalence in England, derived from the National Cancer Registration and Analysis Service, was used for the comparison of prevalence and types of cancer in the background adult female population. This registry included patient data for the period of 1995–2015 and for people who were alive on 31st December 2015.¹³

Data analysis was performed with SPSS statistical software version 22.0 (SPSS Inc.). The study was approved by OUH NHS Trust Audit committee as a quality improvement project (QIP 3768).

3 | RESULTS

3.1 | Baseline characteristics

In total, 156 women with TS were included. The median age of the population was 32 (range 18–73) years and median age at TS diagnosis was 12 (range 0–62) years. The median time since the diagnosis of TS at the last clinical review was 21 (range 0–54) years. Amongst 152 TS women with an available detailed karyotype, the majority were 45,X (40.8%), and 11 (7.2%) had whole or partial Y chromosome material (Table 2). All women who required HRT received treatment until approximately age 51 years. Nineteen women who had spontaneous menarche did not require HRT initially; however, two of these women required HRT from age 27 and 30 years. Seventy-two (49.3%) received GH treatment; amongst those women who did not receive GH treatment (74/146), 80% had TS diagnosed after 10 years of age. The prevalence of autoimmune diseases was 28.2% (44/156); the majority (36/156) had Hashimoto thyroiditis.

3.2 | Cancer prevalence in the TS cohort

Cancer prevalence in the TS cohort was 9/156 women (5.8%). The median age at cancer diagnosis was 35 (range 7–58) years and median time since the diagnosis of TS and diagnosis of cancer was 23 (–5 to 48) years. The spectrum of cancer diagnosis was broad; bilateral gonadoblastoma (1/9), gastrointestinal neuroendocrine tumours (NET) (2/9), gastric stromal tumour (1/9), plasma cell dyscrasia (1/9), synovial sarcoma (1/9), cervical cancer (1/9), medulloblastoma (1/9) and aplastic anaemia (1/9). Detailed clinical characteristics of the patients with a cancer diagnosis are presented in Table 3. The 45,X karyotype was the predominant, seen in five patients with cancer. Two cancers were detected incidentally, whilst cervical cancer was detected during routine screening and bilateral gonadoblastoma was detected in 1 of the 11 patients with Y chromosome materials who had prophylactic gonadectomy. Three women received GH treatment during their childhood, and all women who were aged below the mean age of menopause had been receiving HRT. Four patients had autoimmune disease. No significant association between cancer occurrence and karyotype, HRT use, GH use and autoimmune diseases was noted.

TABLE 1 Summary of population studies published on overall cancer occurrence in TS.

Study	Year of study publication	Number of patients with TS	Number of patients with cancer diagnosis	Median age at cancer diagnosis (years)	Cancer prevalence (%)	TS cancer risk compared with background population			
						Increased	Relative risk (95% CI)	Decreased	Relative risk (95% CI)
Viuff et al. ¹⁰	2020	1156	56	53.9	4.8	Cancer		Cancer	
						Total cohort			
						- Colo-rectal cancers	2.41 (1.32–4.39)	- Breast cancer	0.44 (0.22–0.88)
						- non-melanoma skin cancers	2.23 (1.19–4.17)		
						- Benign skin neoplasms	2.03 (1.42–2.90)		
						45,X Subgroup			
						- Colo-rectal cancers	3.07 (1.14–8.33)		
						- Non-melanoma skin cancers	5.38 (2.63–10.98)		
						- Benign skin neoplasms	3.20 (2.04–4.99)		
						45,X/46, XX subgroup			
Ji et al. ²	2016	1409	70	Not reported	4.9	- Colo-rectal cancers	3.24 (1.19–8.81)		
						- Solid tumours	1.32 (1.02–1.67)	- Breast and female genital organ	0.7 (0.41–1.12)
						- CNS tumour	6.63 (3.98–10.37)		
						- Meningioma	13.99 (7.2–24.5)	- Breast	0.12 (0.01–0.45)
						- Melanoma	3.0 (1.43–5.53)		
						Total cohort			
						- CNS tumours	4.3 (2.3–7.4)	- Breast	0.3 (0.2–0.6)
						- Meningeal tumours	12.0 (4.8–24.8)		
						- Bladder and urethra	4.0 (1.3–9.2)		
						- Vulvo-vaginal cancers	5.3 (1.1–15.3)		
Schoemaker et al. ¹¹	2008	3425	73	Not reported	2.1	- Eye	10.5 (1.3–37.9)		
						45,X Subgroup			
						- CNS tumours	8.2 (3.5–16.2)	- Cervix	0.2 (0.0–1.1)
						- Meningeal tumours	17.9 (3.7–52.3)		

TABLE 3 Characteristics of women with TS with cancer recorded.

Tumour/cancer type	Age at tumour/cancer diagnosis (years)	Cancer presentation	Age at TS diagnosis (years)	Karyotype	HRT duration (years)	GH Treatment	Additional observations
Gastric stromal tumour	58	Incidental	10	45,X	35	No	<ul style="list-style-type: none"> • Coeliac disease • Positive TPO antibodies
Plasma cell dyscrasia with POEM syndrome	38	Lower limb numbness	13	45,X	30	No	<ul style="list-style-type: none"> • Cirrhosis of liver • Addison's disease • Osteopenia
Gastric NET G 1	58	Abdominal pain and dyspepsia	58	45,X(48)/46,X,r(X)(2)	20	No	<ul style="list-style-type: none"> • Primary hypothyroidism • Atrophic gastritis
Synovial sarcoma	55	Chronic hip pain	13	45,X	37	No	<ul style="list-style-type: none"> • Coeliac disease • Positive TPO • Obesity
Cervical cancer	35	Screening programme	12	45,X/46,XY	27	Yes	<ul style="list-style-type: none"> • Impaired glucose tolerance
Medulloblastoma	27	Headaches and vomiting	Pre-natal	45,X/46,Xi(Xq) amniocentesis	15	Yes	<ul style="list-style-type: none"> • Primary hypothyroidism • Osteopenia
Bilateral gonadoblastoma	20	Prophylactic gonadectomy	15	46,XY(16/30)/45,X(14/30)	14	Yes	-
Aplastic anaemia	7	Clinical symptoms of anaemia	12	45,X(9/46)/46,XX(21/46)	None	No	-
Appendix NET	21	Incidental	15	45,X	30	No	<ul style="list-style-type: none"> • Hypertension • Hypercholesterolaemia • Type 2 diabetes • Osteoporosis

Abbreviations: GH, growth hormone; HRT, hormone replacement therapy; NET, neuroendocrine tumour; POEMS, polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy of unknown significance, skin changes; TPO, thyroid peroxidase antibodies; TS, Turner syndrome.

TABLE 4 Cancer prevalence in the background female population.¹³

Cancer type	Cancer prevalence in females, 18+ (%)
All cancers combined	4.41
Bladder	0.06
Brain	0.02
Breast, female	2.16
Cervix uteri	0.14
Colorectal	0.44
Head and neck	0.08
Hodgkin lymphoma	0.04
Kidney, renal pelvis and ureter	0.09
Leukaemia	0.07
Liver	0.01
Lung, trachea and bronchus	0.14
Melanoma of skin	0.31
Mesothelioma	0.002
Multiple myeloma	0.04
Non-Hodgkin lymphoma	0.17
Oesophagus	0.02
Other	0.25
Ovary	0.18
Pancreas	0.02
Stomach	0.02
Uterus	0.32
Unknown primary	0.02

reduced overall survival in TS compared to age-matched controls, with cancers being the third leading cause of death. However, the authors believed that these deaths were likely incidental rather than TS related.¹⁵

However, the above observations were not replicated in larger population studies.^{10–12} Schoemaker MJ. et al., reported cancer incidence in women with TS in the United Kingdom (UK) by analyzing data from National Health Service Central Register (NHSCR) for England and Wales and the NHSCR for Scotland, and they observed 73 malignancies occurred other than non-melanoma skin cancers in 3425 women with TS with no enhanced cancer risk (SIR 0.9 [95% CI 0.7–1.2]).¹¹ Comparably, Viuff et al., observed no overall increase in the cancer risk (prevalence of cancer 4.8% vs. 6.2% in age-matched controls, hazard ratio [HR] 1.04) amongst 1156 women with TS in the recently published Danish National Patient Registry data.¹⁰

4.2 | Spectrum of cancers in TS

The pattern of reported cancers in our cohort differs substantially to the background female population as well as to the previously reported studies in TS. The majority of the patients in the present cohort had very rare cancers (7/9) with reported incidence ranging from 1.2 to 30 cases per million population.^{16–22} None of our patients had one of the commonly reported cancers detected in the background female population such as breast, colo-rectal and uterine cancers; however, one patient had cervical cancer which is the 14th most common cancer identified in females in the UK.²³ Given the very small number of patients with cancer in our cohort, we could not identify any meaningful associations between cancer occurrence and other specific factors, such as karyotype, HRT use, GH use and autoimmune diseases.

One out of 11 patients who had Y chromosome material present was detected to have a gonadoblastoma (9%) following prophylactic gonadectomy. A wide range of prevalence was observed in the rate of gonadoblastoma occurrence in association with overt (22%–43%) or cryptic Y chromosome material (18%–100%) in reported studies that is probably related to the heterogeneity in methodology.⁶ No cases of gonadoblastoma were reported in four out of five aforementioned large population studies; however, the UK cohort observed 5/73 cases with a 7.9% increment in cumulative risk of gonadoblastoma by age 25 years in women with presence of Y chromosome. Gravholt et al., reported a very low rate of occurrence of gonadoblastoma in a population study ($n = 114$); out of 14 patients who had presence of Y chromosome, only 1 patient (10/14 had gonadectomy) had gonadoblastoma.²⁴ However, a recently published multi-centre study from France, that included 70 women with TS with 45,X/46,XY karyotype, observed 9 patients with gonadoblastoma (prevalence 12.8%) out of 58 patients who underwent gonadectomy.²⁵

The risk of central nervous system (CNS) tumours, predominantly meningioma, was consistently elevated in the Swedish² and the UK¹¹ cohorts amongst women with TS. Subgroup analysis of the UK cohort reported increased risk of meningioma in both 45,X and 45,X/46,XX groups whilst the Danish cohort reported elevated risk (HR 3.2 [1.2–8.5] only amongst 45,X karyotype (no increased risk of meningioma was observed in the total cohort)).¹⁰ The relationship between oral contraceptive (OCP) and HRT use and occurrence of meningioma was extensively studied amongst non-TS women without any conclusive evidence.^{26–28} Nevertheless, some cohort studies reported higher risk with oestrogen-only preparations, whilst some meta-analyses suggest elevated risk with HRT use.^{27,28} Despite women with TS being exposed to HRT for a longer time period during their life span compared to the general female population, recently published Danish data failed to show any correlation between HRT use and occurrence of CNS tumours amongst women with TS.¹⁰ Cytogenetic analysis of meningioma has shown that chromosomal instability has been the most frequent molecular alteration that determines tumour recurrence and prognosis.²⁷ Given the consistent

association of meningioma with TS, it can be speculated that haploinsufficiency of X chromosome might have a role in predisposing women with TS to develop meningioma that could be linked to the aforementioned chromosomal instability theory. It is unknown, how these associations behave in the setting of long-term HRT use. In this context of unclear pathophysiological explanation, some suspect that the higher occurrence of meningioma in TS is merely a coincidental observation, given meningioma is the commonest primary CNS tumour with female predominance.^{27,28}

Elevated risk of colorectal cancers (CRCs) has been observed consistently in Danish cohort studies published in different time frames,^{3,10,12} but not in the UK¹¹ or Swedish² cohorts. Subgroup analysis of the recent Danish study showed that elevated risk was seen with both 45,X and 45,X/46,XX karyotypes.¹⁰ In addition to this, Gorrepati et al., identified increased CRC detection rate with colonoscopy amongst women with TS, in comparison to matched controls in a case-control study ($n = 546$).²⁹ Studies conducted amongst the general female population, show some association between oestrogen deficiency state and CRCs. In a case-control study ($n = 1064$), Wernli et al., reported 30%–50% reduction in the risk of CRC with gravidity, whilst 40%–60% increase in the risk with nulligravid state and nulliparity.³⁰ Molecular studies reported that CRCs with high- chromosomal microsatellite instability (MSI) were more likely to be associated with the nulligravid state,³⁰ and the MSI-high state has been related to rapid adenoma-carcinoma progression.²⁹ Moreover, immunohistochemistry analysis of CRCs demonstrated a lack of expression of oestrogen receptor-beta (normally found in colonic epithelium) was associated with advanced tumour stage and poor survival.²⁹ In light of this evidence, it could be postulated that oestrogen deficiency and the nulligravid state associated with TS might increase the risk of CRC and that higher occurrence of MSI-high tumours could be related to haploinsufficiency of X chromosome. Additionally, inflammatory bowel disease is reported to be increased in TS, and in turn could increase the risk of CRC in women with TS.¹² However, the Women's Health Initiative study group and several other observational studies observed an incidental reduction of CRC with HRT in post-menopausal women.³¹ Slattery et al., reporting outcomes of a population-based case-control study, suggested oestrogen exposure in women protects against MSI.³² Hence, given that women with TS are more likely to receive HRT compared to the background female population, they would be expected to be at a reduced risk for CRCs. In summary, a pathophysiological basis for an observed higher risk of CRCs in TS is not yet explained from available evidence. In this context, it could be speculated that the observed high risk of CRCs amongst women with TS could merely be a coincidence, given CRC is the second commonest cancer recorded in the background female population.¹³

Furthermore, increased risk of other cancers was inconsistently reported in the above-mentioned population studies, that is, bladder, urethra, eye and vulvo-vaginal cancers,¹¹ melanoma,² benign skin cancers and tongue cancers.¹⁰ However, their pathophysiological relation to TS is not clear. The 2016 International Guidelines highlight the reported excess incidence of melanoma in TS but equally suggest

this is lower than perhaps expected in view of the heightened number of pigmented naevi in TS.⁷ Furthermore, the guidelines consensus was a lack of cost-effectiveness for any routine cancer screening in TS beyond surveillance for melanoma during follow-up.

In contrast to the discordant results discussed for the different tumours above, all recently reported large population studies consistently observed reduced occurrence of breast cancers in women with TS compared to the background female population.^{2,10,11} Additionally, the UK¹¹ and Swedish² cohorts observed lower frequency of cancers in female genital organs. This is an important observation given the robust evidence to support a positive correlation between long-term HRT use and breast and uterine cancers in non-TS women.⁸ Women with TS are more likely to receive HRT during the full length of their reproductive years, hence this observation at first glance perhaps challenges the existing data (similar to the aforementioned controversy regarding CRC). Investigators of the recent Danish cohort explored the association between HRT use and breast cancer in TS and failed to identify any added risk.¹⁰ Hence, it could be postulated that the relatively low sex hormone state in TS, renders women less prone to hormone-responsive cancers. Women with TS characteristically have hypergonadotrophic hypogonadism. In addition, delayed diagnosis, hence delayed commencement of HRT, significant variation in HRT prescriptions and dose, lack of clear targets of adequate hormone replacement, unmonitored hormone replacement and issues related to compliance could contribute to a relatively insufficient sex hormone state in these patients compared to the background female population. In favour of this hypothesis, Wu et al. reported an inverse association of breast cancer and premature ovarian insufficiency (non-TS) amongst a large group of Chinese women.³³ Future studies that compare occurrence of cancers in TS, in relation to serum oestrogen level may help clarify some of these issues.

4.3 | Strengths and limitations

Whilst our cohort provides 'real world data' in this group, as we have evaluated patients being managed in a single tertiary care centre by the same group of clinicians long term, there are several limitations to our report. These include a relatively small sample size when compared to the reported population studies, historical data from a selected population and lack of data on oestrogen levels and compliance with HRT. Moreover, the comparator background population data are available till 2015, thus any more recent trend in population incidence might in theory be missed. We find a high prevalence of unusual cancers within our cohort which are unlikely to be mechanistically related to TS per se. It is difficult to draw any meaningful conclusion about associations given the very small sample size. However, our data highlight the importance of considering the possibility of non-TS-related aetiologies including tumours as a differential diagnosis for unexplained signs and symptoms or unexpected radiological abnormalities.


5 | CONCLUSIONS

In conclusion, women with TS demonstrate a different pattern of cancer morbidity to the background female population, and this is very likely to relate to the altered sex hormone status and might be usefully further explored in large prospective patient cohorts in relation to serum oestrogen levels and compliance. In the future, it would be important to explore the correlation between different cancer morbidities and commonly associated conditions which are definitely associated with TS such as autoimmune disease, NAFLD and metabolic syndrome. Available data do not show any association between common treatments used in TS, such as HRT and GH, and cancer occurrence. Notably, this study suggests that there is a common incidence of rare often incidentally detected tumours, and that not all abnormal investigations detected during long-term follow-up of a woman with TS are necessarily related to TS itself. Notwithstanding the reduced incidence of common malignancy and in particular hormone responsive malignancies, it is possible that this may change in the future with earlier diagnosis, improved adequacy of HRT, and increased detection rates, thus the education of women with TS to monitor and undergo standard, for example, mammography and cervical smear examination, where indicated is essential in the long-term management of TS.

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