Original Article
Yonsei Med J 2022 Nov;63(11):991-998
https://doi.org/10.3349/ymj.2022.0143
Yonsei Medical Journal
YMJ
pISSN: 0513-5796 · eISSN: 1976-2437

Population Prevalence, Cancer Risk, and Mortality Risk of Turner Syndrome in South Korean Women Based on National Health Insurance Service Data

Sung Eun Kim[1], Sang Hyun Park[2], Kyungdo Han[3], Won Kyoung Cho[4], Byung-Kyu Suh[5], and Yong-Gyu Park[2]

[1]Department of Pediatrics, Incheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul;
[2]Department of Biostatistics, College of Medicine, The Catholic University of Korea, Seoul;
[3]Department of Statistics and Actuarial Science, College of Natural Sciences, Soongsil University, Seoul;
[4]Department of Pediatrics, St. Vincent's Hospital, College of Medicine, The Catholic University of Korea, Seoul;
[5]Department of Pediatrics, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea.

Purpose: In South Korea, investigations into Turner syndrome (TS) prevalence and TS-associated cancer and mortality are lacking. Accurate data were estimated from the National Health Insurance Service (NHIS) and the Rare Diseases Registry (RDR) records.
Materials and Methods: Data on patients with TS who were registered in the RDR between 2007 and 2017 were collected. To estimate TS-associated cancer and mortality risk, the data were compared with data of 1:3 age-matched controls.
Results: In 2017, 2054 patients with TS were identified from a total population of 26186952 South Korean women; therefore, the prevalence was 7.84 per 100000 persons. TS prevalence across 10-year interval age groups were 11.82, 23.17, 18.37, 10.49, 4.09, and 0.38 for age under 10 years, teenagers, 20s, 30s, 40s, and older than 50, respectively (per 100000 persons). The cancer risk in patients with TS was higher than that of age-matched controls over 5.3 person-years [hazard ratio (HR)=1.82, 95% confidence interval (CI) 1.01–3.27, p=0.045]. Among different types of cancer, thyroid cancer risk in patients with TS was significantly higher than that of age-matched controls (HR=2.78, 95% CI 1.06–7.26, p=0.037). We also observed that TS-associated all-cause mortality risk was higher than that of age-matched controls (HR=3.36, 95% CI 1.59–7.10, p=0.002).
Conclusion: National prevalence of TS was suggested, and an increased risk of TS-associated thyroid cancer and mortality were observed in this study.

Key Words: Prevalence, turner syndrome, thyroid cancer risk, mortality risk.

INTRODUCTION

Turner syndrome (TS), first introduced in 1938 by Henry Turner,[1] is defined as a phenotypic female condition with one or more typical clinical features and partial or complete absence of a second X chromosome in karyotyping.[2,3] Although exact rates differ among studies, approximately half of individuals with TS have complete monosomy of the X chromosome. Common physical features of newborn patients with TS are webbing of the neck, protruding ears, and lymphedema of the hands and feet.[4] Among children with TS, valve diseases, such as mitral regurgitation, bicuspid aortic valve, and aortic coarctation, and renal anomalies, such as hydronephrosis and horseshoe kidney, are often reported.[5,6] In adolescents and adults, short stature, amenorrhea, and a lack of secondary sex characteristics are generally common.[7] TS is the most common sexual development disorder with primary amenorrhea.[8]

Since the first diagnosis of TS, epidemiology of this genetic disorder has been thoroughly investigated across various na-

Received: May 9, 2022 **Revised:** August 26, 2022
Accepted: September 5, 2022 **Published online:** October 7, 2022
Co-corresponding authors: Won Kyoung Cho, MD, PhD, Department of Pediatrics, St. Vincent's Hospital, College of Medicine, The Catholic University of Korea, 93 Jungbu-daero, Paldal-gu, Suwon 16247, Korea.
E-mail: wendy626@catholic.ac.kr and
Kyungdo Han, PhD, Department of Statistics and Actuarial Science, College of Natural Sciences, Soongsil University, 369 Sangdo-ro, Dongjak-gu, Seoul 06978, Korea.
E-mail: hkd917@naver.com

•The authors have no potential conflicts of interest to disclose.

tions and ethnic groups, although there is a lack of nationwide studies in Africa, Asia, and South America. Most studies on the epidemiology of TS in Asian countries are old. A Japanese study in 1993 reported an incidence of 1 in 476 live-born females,[9] and a Singapore study in 2009 reported an incidence of 1 in 1176 live-born females.[10] The Singapore study was based on data from 1999 to 2004. A multicenter, but not nationwide, Korean study in 1999 reported 10 TS cases in 11000 samples of amniotic fluid, in which the incidence among live-born females could not be estimated.[11] Although there are ethnic and racial differences, the prevalence of TS is estimated to be approximately 1 in 2500 live-born females.[12] With the recent increase in incidence of TS in female live births, a prevalence of 1 in 1700 live-born females was suggested in a Danish study based on nationwide cytogenetic registry.[13]

Patients with TS face several medical problems throughout their lives. The life expectancy of women with TS is shorter than that of normal women as a result of complications from heart disease and diabetes.[14] Significant increased risks for certain types of cancer, such as nervous system cancer, gastrointestinal cancer, and melanoma, have been reported in patients with TS,[15] and a possible risk of gonadoblastoma was suggested in mosaic TS with Y chromosome.[16] Regarding these issues, epidemiologic data of TS-associated cancer and mortality has been lacking in South Korea.

Since 1989, South Korea has maintained a universal compulsory National Health Insurance Service (NHIS) that offers health care services to nearly 100% of the Korean population.[17] This system not only covers insurance of the population but also maintains records of individual health information. The data of rare and intractable diseases, such as TS, are managed separately in the Rare Disease Registry (RDR) program, initiated by the NHIS in 2004 to support patients suffering from these diseases.[18] Using from the program, TS prevalence and incidence and TS-associated mortality and cancer morbidity in South Korea were estimated in this study.

MATERIALS AND METHODS

The Korean RDR and the NHIS databases

In 2013, the NHIS covered 97.2% (n=49989620) of the Korean population; and the Medical Aid system covered the remaining 2.8% (n=1458871).[19] A nationwide registry for rare and intractable diseases was established in 2001 by the Korean NHIS in cooperation with the Ministry of Health and Welfare.[20] This service system, called RDR, manages lists of patients with rare and/or intractable diseases and provides expanded health insurance services, because managing the diseases is challenging and treatments are generally expensive. Patients with TS have been registered in the RDR (specific code designation V021) since 2002, and actual insurance support became effective in 2007. The RDR database collects specific medical information on all registered patients with a physician-certified diagnosis. Regardless of the initial purpose of collecting and preserving medical records in the RDR system, the data provide information on prevalence and associated morbidity and mortality in these patients. Annual incidences can be calculated from the number of newly registered patients with a certain disease.

From the NHIS claims database (NHIS-2020-1-489), data from patients with TS registered in the RDR between 2007 and 2017 were collected. The total number of registered patients with TS and newly registered patients with TS in each year were counted. By using the entire Korean female population in the resident registration data obtained by the Korean Ministry of Security and Public Administration, the prevalence of patients with TS was calculated.[21] Mortality risk was estimated from population and death data resource profiles in the NHIS database (NHID) individually linked to mortality registration data from Statistics Korea. Under ethics approval from the researchers' Institutional Review Board (IRB), access to the NHID was obtained through the NHIS website (http://nhiss.nhis.or.kr). This study was approved by the IRB of the Catholic University of Korea (IRB Number: KC17EIS10016).

Study subjects

To certify diagnosis of TS, two diagnostic criteria are required by the RDR program. One is the presence of characteristic clinical manifestations of TS, such as certain phenotypic features (webbed neck, low hairline, low-set ears, lymphedema of hand and feet, cubitus valgus), short stature, heart anomaly, amenorrhea, osteoporosis, gonadal tumors, and abnormal thyroid function. The other is karyotype confirmation: a single X chromosome or other karyotypes, such as mosaicism, isochromosome, or ring chromosome of X, is required. The 10th revision of the International Classification of Diseases (ICD) includes codes Q96,0 (Karyotype 45, X), Q96.1 [Karyotype 46, X iso(Xq)], Q96.2 [Karyotype 46, X with abnormal sex chromosome, except iso(Xq)], Q96.3 (Mosaicism, 45, X/46, XX or XY), Q96.4 [Mosaicism, 45, X/other cell line(s) with abnormal sex chromosome], Q96.8 (Turner's syndrome, unspecified Other variants of Turner's syndrome) and Q96.9 (Q96 Turner's syndrome) in V021, the specific RDR designation for TS.

Outcome variables

From 2007 to 2016, 1506 people were newly diagnosed with TS. Fifty-two patients who were diagnosed with cancer before 2010 and 19 patients with 1 year-lag (cancer occurrence or death in the first year of follow-up) were excluded (Fig. 1). A total of 1435 patients with TS were compared with age-matched controls in order to estimate TS-associated cancer and mortality risk. Social income, residential characteristics (rural/urban), and presence of diabetes mellitus (DM) were investigated and adjusted in both the TS group and control group. Residential characteristics and social income reflects socioeconomic sta-

https://doi.org/10.3349/ymj.2022.0143

tus, which has a strong connection to cancer risk[22] and mortality.[23,24] DM is a well-known risk factor for high mortality due to vascular complications,[25] and increased risks for various types of cancer in DM have been suggested.[26] Other factors, such as smoking, obesity, and family history of cancer (genetic tendency), may also be considered as important factors. However, based on similar studies,[21,27,28] we considered income, residence, and DM would be sufficient for interpreting the data. Cancer incidence and mortality are presented as the number of cases per 1000 persons, adjusted in consideration of the observation period (person-years). Frequencies of different types of cancers, including stomach (ICD-10, C16), colorectal (C18-20), liver (C22), pancreatic (C25), lung (C33-34), breast (C50), cervical (C53), thyroid (C73), lymphoma (C82-86), ovarian (C56), oral (C00-14), esophageal (C15), biliary (C24), laryngeal (C32), corpus (C54), renal (C64), bladder (C67), nervous system (C70-72), multiple myeloma (C90), leukemia (C91-95), and skin (C43), were ascertained for both groups in order to assess incidence rates (IR) and hazard ratios (HR) of cancers. The rates are also calculated for the total number of all cancers in both groups. The mortality rates (MR) of both groups were also calculated to compare HRs of death in the subjects and the controls.

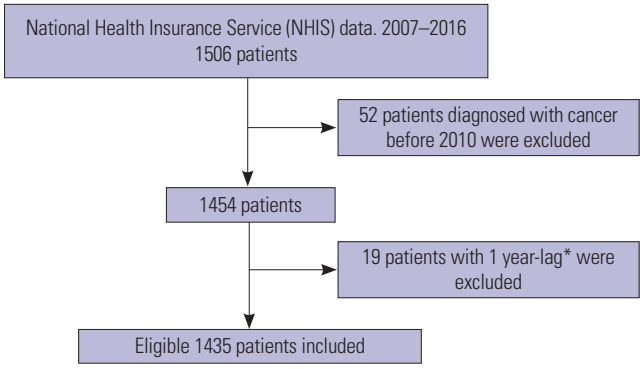

Fig. 1. Flow diagram of study subjects for cancer incidence and mortality.
*Cancer occurrence or death in the first year of follow-up.

Statistical analysis

Given the yearly number of registered and deceased patients with TS in South Korea from 2007 to 2017, newly registered patients with TS in each year were calculated as follows: the total number of patients with TS in a certain year were subtracted by the total number of patients with TS in the previous year, and then, the number of death of patients with TS in the corresponding year were added. After wash-out of year 2006, annual IR of patients with TS from 2007 to 2017 were calculated based on these data. Age standardization across 10 year-intervals was conducted by adjusting prevalence and IR to the Korean population in the middle of year 2010 (direct method), provided by Statistics Korea. Prevalence in 2017 was subdivided across different age groups at 10-year intervals. As for cancer incidence and mortality, 1:3 age-matched controls (total n=4305) were selected randomly from the NHID in the period between 2007 and 2017. IRs of cancer and MRs in both groups were calculated by dividing the incidence of cancer and death by the total follow-up period from 2007 to 2017, respectively. Multivariable Cox regression models were used to assess the HRs of cancer and death for both groups. 95% confidential intervals (CIs) for HRs are presented as means [mean -1.96 standard error (SE), mean +1.96 SE], and p values≤0.05 were considered statistically significant. All analyses were conducted using SAS software version 9.4 (SAS Institute, Cary, NC, USA).

RESULTS

Population prevalence and incidence of TS in South Korea

The annual prevalence and incidence of TS in South Korea from 2007 to 2017 are presented in Table 1. The total number of cases was counted from the total female population in South Korea. Prevalence/incidence per 100000 persons and age standardization prevalence/incidence were also calculated. Prevalences per 100000 persons in 2007, 2008, 2009, 2010, 2011,

Table 1. Prevalence and Incidence of Turner Syndrome in South Korea

Year	Population	Total number of registered-cases	Prevalence per 100000 persons	Age standardization* prevalence	Number of newly-registered cases	Incidence per 100000 persons	Age standardization incidence
2007	24200931	1269	5.24	4.91	165	0.65	0.69
2008	24698959	1364	5.52	5.24	179	0.68	0.72
2009	24860650	1454	5.85	5.63	176	0.68	0.71
2010	25012543	1346	5.38	5.28	127	0.50	0.51
2011	25160402	1498	5.95	5.95	174	0.70	0.69
2012	25522008	1592	6.24	6.59	146	0.57	0.61
2013	25668348	1706	6.65	7.15	132	0.51	0.56
2014	25822173	1816	7.03	7.73	138	0.53	0.59
2015	25968809	1879	7.24	8.11	137	0.53	0.59
2016	26097935	1981	7.59	8.61	131	0.50	0.57
2017	26186952	2054	7.84	9.06	125	0.48	0.56

*Age standardization was conducted based on the Korean population for the middle of year 2010, provided by Statistics Korea.

2012, 2013, 2014, 2015, 2016, and 2017 were 5.24, 5.52, 5.85, 5.38, 5.95, 6.24, 6.65, 7.03, 7.24, 7.59, and 7.84, respectively, showing an increasing trend each year. Incidences per 100000 persons in 2007, 2008, 2009, 2010, 2011, 2012, 2013, 2014, 2015, 2016, and 2017 were 0.65, 0.68, 0.68, 0.50, 0.70, 0.57, 0.51, 0.53, 0.53, 0.50, and 0.48, respectively, maintaining a number around 0.5–0.7 per 100000 persons each year.

Prevalence and incidence distribution of TS across 10-year interval age groups in 2017

Age distributions of TS in 2017 are presented in Table 2. Patients with TS in 2017 are grouped according to their age by 10-year intervals from age under 10 to 50s. Prevalences of TS per 100000 persons in 0- to 9-year-olds, 10- to 19-year-olds, 20- to 29-year-olds, 30- to 39-year-olds, 40- to 49-year-olds, and 50 and over were 11.82, 23.17, 18.37, 10.49, 4.09, and 0.38, respectively. Overall, the prevalence of TS showed normal distribution; the highest prevalence was in teenagers and the second highest in 20s. Most of the patients with TS were younger than 40. The prevalence per 100000 persons in age between 0 to 39 was 15.72, whereas the prevalence per 100000 in age 40 and over was 1.49. The incidence of TS per 100000 persons in 0- to 9-year-olds, 10- to 19-year-olds, 20- to 29-year-olds, 30- to 39-year-olds, 40- to 49-year-olds, and 50 and over were 1.91, 1.75, 0.46, 0.27, 0.09, and 0.07, respectively. A total of 0.48 per 100000 persons were diagnosed with TS in 2017. Eighty percent of the incident cases were found before age of 20, while less than 5 percent were diagnosed after 40.

Incidence of cancer in patients with TS compared with age-matched controls from 2007 to 2017

Twenty-four individual types of cancer (stomach, colorectal, liver, pancreatic, lung, breast, cervical, thyroid, lymphoma, ovarian, oral, esophageal, biliary, laryngeal, corpus, renal, bladder, nervous system, multiple myeloma, leukemia, and skin) and cancers-in-total were analyzed in this study. The results of cancers-in-total, breast, ovarian, nerve, bladder, and thyroid cancer are presented in Table 3. The IRs of all types of cancer per 1000 persons in the control and TS groups were 1.36 and 2.40, respectively. The adjusted HR of TS for all types of cancer was 1.82 (95% CI 1.01–3.27, p=0.045), showing a difference when compared to the control group. No significant differences were found in breast and ovarian cancer. There were two cases of nerve cancer and one case of bladder cancer, but HRs were not

Table 2. Prevalence and Incidence of Turner Syndrome Distribution Across 10-Year Age Groups in 2017

Age	Population	Total Number of cases	Prevalence per 100000 persons	Total number of incidence	Incidence per 100000 persons
0–9	2173716	257	11.82	43	1.91
10–19	2546817	590	23.17	46	1.75
20–29	3293140	605	18.37	15	0.46
30–39	3681152	386	10.49	10	0.27
40–49	4332041	177	4.09	4	0.09
50–	10160086	39	0.38	7	0.07

Table 3. HRs of Cancer in Patients with TS and Age-Matched Controls from 2007 to 2017

			n	Event	Duration (person-years)	IR (per 1000 persons)	HR (95% CI) unadjusted	p value	HR (95% CI) adjusted*	p value
All cancer		Control	4305	31	22751.64	1.36	1		1	
		TS	1435	18	7504.22	2.40	1.76 (0.99–3.15)	0.056	1.82 (1.01–3.27)	0.045
Breast cancer		Control	4305	8	22833.77	0.35	1		1	
		TS	1435	3	7563.84	0.40	1.13 (0.30–4.26)	0.855	1.24 (0.33–4.68)	0.749
Ovarian cancer		Control	4305	1	22854.87	0.04	1		1	
		TS	1435	1	7570.24	0.13	3.01 (0.19–48.17)	0.435	2.91 (0.18–46.89)	0.452
Nerve cancer		Control	4305	0	22833.77	0	1		1	
		TS	1435	2	7563.84	0.26	-	-	-	-
Bladder		Control	4305	0	22854.87	0	1		1	
		TS	1435	1	7570.24	0.13	-	-	-	-
Thyroid cancer		Control	4305	9	22815.68	0.39	1		1	
		TS	1435	8	7532.40	1.06	2.69 (1.04–6.97)	0.042	2.78 (1.06–7.26)	0.037
Thyroid cancer in TS by age group	0–19	Control	2910	1	14782.95	0.07	1		1	
		TS	970	1	4917.03	0.20	3.01 (0.19–48.15)	0.436	3.09 (0.19–49.53)	0.424
	20–	Control	1395	8	8032.73	1.00	1		1	
		TS	465	7	2615.37	2.68	2.67 (0.97–7.37)	0.058	2.86 (1.03–8.08)	0.047

DM, diabetes mellitus; TS, Turner syndrome; IR, incidence rate; HR, hazard ratio; CI, confidence interval.
*Adjusted for residence, income, and DM.

https://doi.org/10.3349/ymj.2022.0143

calculated because there was no corresponding case among the controls. Patients with TS exhibited a high risk of having thyroid cancer (adjusted HR=2.78, 95% CI 1.06–7.26, p=0.037). When subdivided by age, thyroid cancer risk in TS increased only in women aged over 20 years (adjusted HR=2.86, 95% CI 1.03–8.08, p=0.047).

Mortality of patients with TS compared with age-matched controls from 2007 to 2017

There were 16 cases of death among 1435 patients with TS (Table 4). Three deaths occurred in patients with TS aged 0–19 years for a MR (per 1000 persons) of 0.61. Three deaths occurred in patients with TS aged 20–39 years (MR=1.42). Ten deaths occurred in patients with TS aged 40 years or older (MR=18.60). Similar to Table 3, adjustment and calculation were performed to assess HRs for death in patients with TS. The HR for death in the TS group was 3.36 (95% CI 1.59–7.10, p=0.002), demonstrating that the patients with TS had a higher risk of death than the control group. The risk was found to be higher in those over 40 years for an HR of 6.51 (95% CI 2.19–19.32, p<0.001). Mortality in those under 20, however, showed no statistical difference from the control group (adjusted HR=3.07, 95% CI 0.62–15.21, p= 0.169).

DISCUSSION

The prevalence of TS per 100000 persons in South Korea increased from 5.24 in 2007 to 7.84 in 2017. At the same time, the IRs of TS per 100000 populations were 0.65 and 0.48, respectively. Prevalence distribution of TS across 10-year interval age groups in 2017 showed a peak prevalence in teenage years, and it started to decrease after 20s. As for cancers, there was high risk of having thyroid cancer in patients with TS. Mortality was significantly high in patients with TS after the age of 40.

The epidemiology of TS has been thoroughly investigated in Europe and America. In Denmark, TS population prevalence was 59 per 100000 newborn females in 2014.[13] In Sweden, TS population prevalence was 30 per 100000 females as estimated crudely by a study investigating TS-associated cancer risk.[29] Among the British population, a crude prevalence estimate of 17 patients with TS per 100000 females was reported based on a population-based study of cancer incidence.[30] In another British study reported in 2017, single nucleotide polymorphism array data from the UK Biobank were analyzed. The corresponding TS prevalence was 88 per 100000 females, the highest prevalence among TS epidemiology studies.[31] 45,X/46,XX mosaicism presumably accounted for this result, and the statistical reliability of the data was limited due to lack of "healthy volunteers." In the United States, the National Organization of Rare Disease estimated that more than 70000 women and girls have TS, approximately 21 cases per 100000 females.[32] As far as we know, there have been no recent studies on the national prevalence of TS in Asia. A study of prevalence of TS in several regions of China was recently conducted in 2018, and various prevalences ranging from 25 to 210 per 100000 females were reported.[33] Overall, the prevalence of TS in South Korea was considerably lower than that of Europe and the United States. While it is difficult to explain this discrepancy with one clear reason, one presumable reason may be the absence of a national screening system for TS. This may lead to lower participation of parents in screening suspected children.

Although the prevalence of TS in South Korea was comparatively lower than that in other studies on TS prevalence, the prevalence trend with age coincides with epidemiologic studies conducted in Europe and the United States. A Danish national cohort study published in 2019 reported that the median age for diagnosis of TS was 15.1 (range: 0.0–85.4) and that the prevalence of TS was highest in teenagers.[13] A study conducted at a single center in the United Kingdom reported that half of patients with TS were diagnosed after the age of 5 years.[34] Delayed diagnosis of TS with an average age of 12.8 years was observed in a study in the United States.[35] Delayed diagnosis of TS in South Korea was evident in our study. As seen in the incidence trend of patients with TS in 2017, 43 patients were newly diagnosed before 10 years, and 46 patients were newly diagnosed as teenagers. Nearly 30% (36 patients) of the total number were diagnosed after an age of 20 years. Furthermore, al-

Table 4. HRs of Death in Patients with TS and Age-Matched Controls from 2007 to 2017

			n	Event	Duration (person-years)	MR (per 1000 persons)	HR (95% CI) unadjusted	p value	HR (95% CI) adjusted*	p value
All cause of death		Control	4305	13	22855.52	0.57	1		1	
		TS	1435	16	7571.16	2.11	3.72 (1.79–7.73)	<0.001	3.36 (1.59–7.10)	0.002
Death in TS by age	0–19	Control	2910	3	14786.09	0.20	1		1	
		TS	970	3	4917.83	0.61	3.01 (0.61–14.89)	0.178	3.07 (0.62–15.21)	0.169
	20–39	Control	1074	5	6372.98	0.78	1		1	
		TS	358	3	2115.72	1.42	1.81 (0.43–7.59)	0.415	0.36 (0.05–2.63)	0.312
	≥40	Control	321	5	1696.45	2.95	1		1	
		TS	107	10	537.61	18.60	6.33 (2.16–18.52)	<0.001	6.51 (2.19–19.32)	<0.001

DM, diabetes mellitus; TS, Turner syndrome; MR, mortality rate; HR, hazard ratio; CI, confidence interval.
*Adjusted for residence, income, and DM.

though not included in Table 2, the same data for years 2015 and 2016 were 37% and 25%, respectively. The falling prevalence trend for TS in those 30 years or older can possibly be explained by relatively fewer cases of newly diagnosed TS after an age of 30 years. Although the annual prevalence of TS is increasing, most newly diagnosed cases of TS are younger than 30, and this implies that many patients with TS over 30 years live undiagnosed. The prevalence was less than 1 per 100000 persons (0.38) in those 50 years and over, probably owing to short life expectancy of patients with TS. TS has a life expectancy that is reduced by up to 13 years and shows a three-fold increase in overall mortality.[13,14] In this study, the HR for mortality in patients with TS was 3.42, consistent with ratios in the aforementioned studies. Since this study was based on data from the NHIS, the detailed causes of death in patients with TS are absent, which should be clarified to find major cause of increased mortality. We presume possible causes for the increased mortality, as discussed earlier, would be heart diseases, and a study in Korea suggested the possibility of impaired vascular function of aorta in teenage TS.[36] The TS-associated mortality HR in those 40 years and over was 6.51, more than double that of patients under 20 (3.07). This discrepancy supplements the explanation for the dramatic fall in TS prevalence in those 40 years and over, with a remarkable decrease in those 50 years and over. Accordingly, medical management of TS needs to be focused on decreasing the MR, especially in those 20 years and older. Modes of surveillance to manage patients with TS should be envisioned with succeeding comprehensive medical care for their comorbidities.

Regarding TS comorbidity, this study showed an increased risk of cancer occurrence in patients with TS, compared to the control group (Table 3). Among different types of cancer, risk of thyroid cancer occurrence was notably high in this study, suggesting a positive correlation between thyroid cancer and TS. Many previous studies have discussed TS-associated cancer risk, and the issue of whether TS increases risk of cancer is still controversial. A British national cohort study of 4909 women with TS reported an insignificant association between cancer risk and TS, inconsistent with the results reported in this study.[30] The British study reported an increased risk of specific tumors, such as brain or urogenital tumors, but only one case of thyroid cancer was reported among 73 malignancy cases in TS. An Italian study that surveyed the prevalence of different types of neoplasia in TS reported an increased risk of skin neoplasm/cancer, CNS tumor, while thyroid cancer occurred in only one of 87 women with TS.[37] Consistently, two other European studies reported correlation of TS with skin neoplasm and brain tumor.[38,39] The main reason for the notably high incidence of thyroid cancer among individuals with TS in South Korea would be the high incidence of thyroid cancer among all Korean women, regardless of having TS. With readily available thyroid screening, the incidence of thyroid cancer in Korean women in 2010 was 111.3 per 100000 persons, 10-fold higher than the average global IR.[40] To our knowledge, there is no other Asian study that has reported IRs for cancer in TS. Future studies of this may provide some clues on racial differences in TS. In addition, another possible explanation for the increased thyroid cancer risk observed in this study may be the predisposition of patients with TS to autoimmune diseases of the thyroid. Haploinsufficiency of X chromosome in TS may be confer susceptibility to autoimmune diseases.[41] Although the exact mechanism remains unclear, autoimmunity involving the thyroid gland has been suggested as a cause of thyroid cancer in previous studies.[42-44] Most of the thyroid cancer cases in this study were diagnosed after 20 years, which coincides with the age distribution of thyroid cancer in the general population of South Korea. There is also a concern for ovarian gonadoblastoma in TS with Y chromosome, either overt or cryptic. A Korean study conducted in 2017 revealed that 12.9% (16/124) of patients with TS had Y chromosomes on karyotyping or Y chromosome material on polymerase chain reaction, and 18.8% (3/16) of them were diagnosed with gonadoblastoma.[45] Since this study was based on registry data under certain diagnostic codes, the exact proportion of patients with TS with Y chromosome material was not found. Therefore, the study could not provide data on the risk of gonadoblastoma in patients with TS.

This study investigated the epidemiology of TS from 2007 to 2017 based on the NHIS and the RDR, national registries that reflect nearly 100% of the entire female population in South Korea. A long period of follow-up with a maximum of 10 years was covered in this research, and this may be representative of national status. In addition, to the best of our knowledge, this study is the largest study of TS epidemiology conducted in Asia. Other large-scaled Asian studies on TS epidemiology are necessary to elucidate definite epidemiological properties among Asians. Further studies might suggest ethnic differences in TS that were previously obscure. In conclusion, this study presents the national prevalence of TS for Korea and a substantially increased risk of TS-associated thyroid cancer and mortality, the reason for which should be clarified through further studies.

DATA AVAILABILITY

All files used for analysis in the present study are available at the National Health Insurance Service sharing service webpage (https://nhiss.nhis.or.kr). Raw data requests can be made through the homepage.

ACKNOWLEDGEMENTS

The authors wish to acknowledge financial support from St. Vincent's Hospital, Research Institute of Medical Science Foundation (SVHR-2020-14) and a grant from the Department of Pediatrics, College of Medicine, The Catholic University of Korea in 2020.

We thank all physicians who contributed their patient data

https://doi.org/10.3349/ymj.2022.0143

to the Korean Rare Disease Registry and the National Health Insurance Service databases.

AUTHOR CONTRIBUTIONS

Conceptualization: Won Kyoung Cho and Sung Eun Kim. Data curation: Sang Hyun Park. Formal analysis: Kyungdo Han. Funding acquisition: Won Kyoung Cho. Investigation: Kyungdo Han. Methodology: Won Kyoung Cho. Project administration: Won Kyoung Cho and Kyungdo Han. Resources: Kyungdo Han and Yong-Gyu Park. Software: Sang Hyun Park. Supervision: Byung-Kyu Suh and Yong-Gyu Park. Validation: Sung Eun Kim, Won Kyoung Cho, and Byung-Kyu Suh. Visualization: Sang Hyun Park. Writing—original draft: Sung Eun Kim. Writing—review & editing: Sung Eun Kim. Approval of final manuscript: all authors.

ORCID iDs

Sung Eun Kim https://orcid.org/0000-0002-1598-3500
Sang Hyun Park https://orcid.org/0000-0003-0612-2562
Kyungdo Han https://orcid.org/0000-0002-6096-1263
Won Kyoung Cho https://orcid.org/0000-0003-0918-0565
Byung-Kyu Suh https://orcid.org/0000-0003-1971-0232
Yong-Gyu Park https://orcid.org/0000-0002-8721-3230

REFERENCES

1. Classic pages in obstetrics and gynecology by Henry H. Turner. A syndrome of infantilism, congenital webbed neck, and cubitus valgus. Endocrinology, vol. 23, pp. 566-574, 1938. Am J Obstet Gynecol 1972;113:279.
2. Bondy CA. Care of girls and women with Turner syndrome: a guideline of the Turner Syndrome Study Group. J Clin Endocrinol Metab 2007;92:10-25.
3. Gravholt CH, Andersen NH, Conway GS, Dekkers OM, Geffner ME, Klein KO, et al. Clinical practice guidelines for the care of girls and women with Turner syndrome: proceedings from the 2016 Cincinnati International Turner Syndrome Meeting. Eur J Endocrinol 2017;177:G1-70.
4. Paolucci DG, Bamba V. Turner syndrome: care of the patient: birth to late adolescence. Pediatr Endocrinol Rev 2017;14(Suppl 2):454-61.
5. Carvalho AB, Guerra Júnior G, Baptista MT, de Faria AP, Marini SH, Guerra AT. Cardiovascular and renal anomalies in Turner syndrome. Rev Assoc Med Bras (1992) 2010;56:655-9.
6. Ko JM. Genetic syndromes associated with congenital heart disease. Korean Circ J 2015;45:357-61.
7. Massa G, Verlinde F, De Schepper J, Thomas M, Bourguignon JP, Craen M, et al. Trends in age at diagnosis of Turner syndrome. Arch Dis Child 2005;90:267-8.
8. Markosyan R. Patients with disorders of sex development. Ann Pediatr Endocrinol Metab 2021;26:74-9.
9. Imaizumi K, Kuroki Y. Prevalence of Turner syndrome in Japan. In: Hibi I, Takano K, editors. Basic and clinical approach to Turner syndrome. Amsterdam: Excerpta Medica; 1993. p.3-6.
10. Tan KB, Yeo GS. Pattern of Turner syndrome in Singapore (1999-2004). Singapore Med J 2009;50:587-90.
11. Yang YH, Ju KS, Kim SB, Cho YH, Lee JH, Lee SH, et al. The Korean collaborative study on 11000 prenatal genetic amniocentesis. Yonsei Med J 1999;40:460-6.
12. Nielsen J, Wohlert M. Chromosome abnormalities found among 34910 newborn children: results from a 13-year incidence study in Arhus, Denmark. Hum Genet 1991;87:81-3.
13. Berglund A, Viuff MH, Skakkebæk A, Chang S, Stochholm K, Gravholt CH. Changes in the cohort composition of Turner syndrome and severe non-diagnosis of Klinefelter, 47,XXX and 47,XYY syndrome: a nationwide cohort study. Orphanet J Rare Dis 2019;14:16.
14. Gravholt CH, Juul S, Naeraa RW, Hansen J. Morbidity in Turner syndrome. J Clin Epidemiol 1998;51:147-58.
15. Berglund A, Stochholm K, Gravholt CH. The epidemiology of sex chromosome abnormalities. Am J Med Genet C Semin Med Genet 2020;184:202-15.
16. Mazzanti L, Cicognani A, Baldazzi L, Bergamaschi R, Scarano E, Strocchi S, et al. Gonadoblastoma in Turner syndrome and Y-chromosome-derived material. Am J Med Genet A 2005;135:150-4.
17. Seong SC, Kim YY, Khang YH, Park JH, Kang HJ, Lee H, et al. Data resource profile: the national health information database of the National Health Insurance Service in South Korea. Int J Epidemiol 2017;46:799-800.
18. Kim HS, Lyoo CH, Lee PH, Kim SJ, Park MY, Ma HI, et al. Current status of Huntington's disease in Korea: a nationwide survey and national registry analysis. J Mov Disord 2015;8:14-20.
19. Song SO, Jung CH, Song YD, Park CY, Kwon HS, Cha BS, et al. Background and data configuration process of a nationwide population-based study using the Korean National Health Insurance system. Diabetes Metab J 2014;38:395-403.
20. Lim SS, Lee W, Kim YK, Kim J, Park JH, Park BR, et al. The cumulative incidence and trends of rare diseases in South Korea: a nationwide study of the administrative data from the National Health Insurance Service database from 2011-2015. Orphanet J Rare Dis 2019;14:49.
21. Cho WK, Lee NY, Han K, Suh BK, Park YG. The population prevalence, associations of congenital heart defect and mortality risk for Down's syndrome in South Korea based on National Health Insurance Service (NHIS) data. Clin Epidemiol 2020;12:519-25.
22. Faggiano F, Partanen T, Kogevinas M, Boffetta P. Socioeconomic differences in cancer incidence and mortality. IARC Sci Publ 1997;138:65-176.
23. Hajat A, Kaufman JS, Rose KM, Siddiqi A, Thomas JC. Long-term effects of wealth on mortality and self-rated health status. Am J Epidemiol 2011;173:192-200.
24. Lantz PM, Golberstein E, House JS, Morenoff J. Socioeconomic and behavioral risk factors for mortality in a national 19-year prospective study of U.S. adults. Soc Sci Med 2010;70:1558-66.
25. Saeedi P, Salpea P, Karuranga S, Petersohn I, Malanda B, Gregg EW, et al. Mortality attributable to diabetes in 20-79 years old adults, 2019 estimates: results from the International Diabetes Federation Diabetes Atlas, 9th edition. Diabetes Res Clin Pract 2020;162:108086.
26. Qi J, He P, Yao H, Song R, Ma C, Cao M, et al. Cancer risk among patients with type 2 diabetes: a real-world study in Shanghai, China. J Diabetes 2019;11:878-83.
27. Kim SU, Ahn S, Lee JE, Han KD, Park SH, Yang SH. Epidemiological study of malignant gliomas in Korea using nationwide dataset from 2007 to 2017. J Korean Med Sci 2021;36:e68.
28. Myung J, Choi JH, Yi JH, Kim I. Cancer incidence according to the National Health Information Database in Korean patients with end-stage renal disease receiving hemodialysis. Korean J Intern Med 2020;35:1210-9.
29. Ji J, Zöller B, Sundquist J, Sundquist K. Risk of solid tumors and hematological malignancy in persons with Turner and Klinefelter syndromes: a national cohort study. Int J Cancer 2016;139:754-8.
30. Schoemaker MJ, Swerdlow AJ, Higgins CD, Wright AF, Jacobs PA.

Cancer incidence in women with Turner syndrome in Great Britain: a national cohort study. Lancet Oncol 2008;9:239-46.
31. Fry A, Littlejohns TJ, Sudlow C, Doherty N, Adamska L, Sprosen T, et al. Comparison of sociodemographic and health-related characteristics of UK Biobank participants with those of the general populationn. Am J Epidemiol 2017;186:1026-34.
32. Sandberg DE, Singer D, Bugajski B, Gebremariam A, Scerbak T, Dooley Maley KL, et al. Research priorities of people living with Turner syndrome. Am J Med Genet C Semin Med Genet 2019;181:43-51.
33. Cui X, Cui Y, Shi L, Luan J, Zhou X, Han J. A basic understanding of Turner syndrome: incidence, complications, diagnosis, and treatment. Intractable Rare Dis Res 2018;7:223-8.
34. Apperley L, Das U, Ramakrishnan R, Dharmaraj P, Blair J, Didi M, et al. Mode of clinical presentation and delayed diagnosis of Turner syndrome: a single Centre UK study. Int J Pediatr Endocrinol 2018;2018:4.
35. Sutton EJ, McInerney-Leo A, Bondy CA, Gollust SE, King D, Biesecker B. Turner syndrome: four challenges across the lifespan. Am J Med Genet A 2005;139A:57-66.
36. An HS, Baek JS, Kim GB, Lee YA, Song MK, Kwon BS, et al. Impaired vascular function of the aorta in adolescents with Turner syndrome. Pediatr Cardiol 2017;38:20-6.
37. Larizza D, Albanesi M, De Silvestri A, Accordino G, Brazzelli V, Maffè GC, et al. Neoplasia in Turner syndrome. The importance of clinical and screening practices during follow-up. Eur J Med Genet 2016;59:269-73.
38. Dejonckheere C, Moyson C, de Zegher F, Antonio L, Van Buggenhout G, Decallonne B. Neoplasia in Turner syndrome: a retrospective cohort study in a tertiary referral centre in Belgium. Acta Clin Belg 2022;77:86-92.
39. Viuff MH, Stochholm K, Lin A, Berglund A, Juul S, Gravholt CH. Cancer occurrence in Turner syndrome and the effect of sex hormone substitution therapy. Eur J Endocrinol 2021;184:79-88.
40. Ahn HS, Kim HJ, Kim KH, Lee YS, Han SJ, Kim Y, et al. Thyroid cancer screening in South Korea increases detection of papillary cancers with no impact on other subtypes or thyroid cancer mortality. Thyroid 2016;26:1535-40.
41. Wegiel M, Antosz A, Gieburowska J, Szeliga K, Hankus M, Grzybowska-Chlebowczyk U, et al. Autoimmunity predisposition in girls with Turner syndrome. Front Endocrinol (Lausanne) 2019;10:511.
42. Feldt-Rasmussen U. Hashimoto's thyroiditis as a risk factor for thyroid cancer. Curr Opin Endocrinol Diabetes Obes 2020;27:364-71.
43. Jackson D, Handelsman RS, Farrá JC, Lew JI. Increased incidental thyroid cancer in patients with subclinical chronic lymphocytic thyroiditis. J Surg Res 2020;245:115-8.
44. Noureldine SI, Tufano RP. Association of Hashimoto's thyroiditis and thyroid cancer. Curr Opin Oncol 2015;27:21-5.
45. Kwon A, Hyun SE, Jung MK, Chae HW, Lee WJ, Kim TH, et al. Risk of gonadoblastoma development in patients with Turner syndrome with cryptic Y chromosome material. Horm Cancer 2017;8:166-73.

https://doi.org/10.3349/ymj.2022.0143