

Unusual Features of Thyroid Carcinomas in Japanese Patients with Werner Syndrome and Possible Genotype–Phenotype Relations to Cell Type and Race

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BACKGROUND. Werner syndrome (WS), an autosomal recessive disease characterized by premature aging, has a high frequency of association with six rare neoplasms in Japanese patients, and only four of these neoplasms also occur excessively in whites. Several differ from what is usual in their epidemiology and/or histology. Described in this article are peculiarities in the occurrences of follicular and papillary thyroid carcinomas among Japanese patients and the possible genotype–phenotype relations pertaining to cell types and the absence of excess thyroid carcinoma occurrence in whites with WS.

METHODS. Epidemiologic features of 23 histologically diagnosed thyroid carcinomas from a series of 150 cancers in 845 Japanese patients with WS were compared with those of 19,446 tumors in a Japanese national registry of thyroid carcinomas from 1977–1991. Germline mutations had been determined by molecular studies of peripheral blood.

RESULTS. The average age of patients with thyroid carcinoma was 39 years for those with WS and 49 years for the registry patients. The female-to-male ratios were 2.3 : 1 and 6.6 : 1, respectively. The rates of occurrence of papillary, follicular, and anaplastic carcinomas were 35%, 48%, and 13% for Japanese patients with WS and 78%, 14%, and 2% in the general Japanese population. All four cases of follicular carcinoma had germline mutations of the WS gene in the C-terminal region, and the germline mutation for the only papillary carcinoma was in the N-terminal region.

CONCLUSIONS. This study suggests two possible WS genotype–phenotype relations. One concerns thyroid carcinoma histology; the other concerns frequent mutations that occur in the C-terminal region in Japanese patients, but not in white patients, with WS. These may account for the excess thyroid carcinoma occurrence among Japanese. *Cancer* 1999;85:1345–52. © 1999 American Cancer Society.

KEYWORDS: Werner syndrome, genetic disease, cancer-prone disease, thyroid carcinoma, genotype–phenotype relation, racial differences.

Werner syndrome (WS) is an autosomal recessive disease characterized by premature aging (bilateral cataracts, gray hair, and skin atrophy).^{1,2} Linkage analysis revealed that the WS gene (WRN) was localized to the short arm of chromosome 8 (8p11–21)³ and was cloned in 1996.⁴ Using worldwide publications (most in the Japanese language) and our own cases, we previously found that the syndrome was associated with a remarkable excess of rare tumors. These included bone and soft tissue sarcomas, myeloid disorders, and benign meningiomas among Japanese and whites, and, among Japanese only, excesses of acral lentiginous melanomas and thyroid carcinomas.⁵ It is noteworthy that carcinomas that often affect the elderly,

TABLE 1
Cases with Werner Syndrome (WS) and Thyroid Carcinoma

Case no.	Patient no.	Age (yrs) at thyroid ca. diagnosis	Gender	Histology of thyroid ca.	Tumors in other organs (age)	Mutation	Thyroid function and other remarks	Reference no.
1	20001	27	F	F	OS (35), Uterine cancer (34)	—	n.d. Struma.	13
2	21201	32	F	F	—	—	n.d. Lung metastasis.	14
3	5501	33	F	F	—	—	n.d. Struma.	15
4	20601	33	M	F ^a	Erythroleukemia (34)	—	n.d. Size: 18 mm.	16
5	21301	37	M	F	Leiomyosarcoma (51)	—	Normal. Struma, elastic firm.	17
6	12501	39	M	F	MFH (40)	1/4	n.d.	18 and p.c. (Dr. T. Azumi)
7	0702	40	F	F	—	4/4	n.d.	1
8	6201	42	F	F	—	7/7	n.d.	p.c. (Dr. H. Matsuno)
9	5001	44	F	F	—	4/4	n.d. Size: 45 × 30 mm.	19
10	20401	44	F	F	—	—	n.d. Struma.	20
11	21401	47	F	F	—	—	Normal, but markedly increased thyroglobulin (17200 ng/mL). ^b Struma.	21
12	6801	27	F	P	—	??	n.d.	22
13	20901	30	F	P	—	—	Normal.	23
14	29101	31	F	P	MDS→AML (40)	—	n.d. Struma.	24
15	20801	36	M	P	SqCC of unknown origin (38)	—	Normal. Struma.	25
16	21501	39	F	P	—	—	Normal, but increased thyroglobulin (260 ng/mL). ^b Struma.	21
17	20101	40	F	P	OS (49)	—	n.d. Struma.	26
18	6901	43	F	P	Meningioma (44)	6/6	n.d. Struma.	27
19	21601	46	M	P	Meningioma (46)	—	Normal, but increased thyroglobulin (451 ng/mL). ^b Size: 15 mm.	28
20	20701	31	M	A	—	—	Normal. Struma. Glioblastoma and thyroid cystic adenoma in a WS brother (age 26 yrs).	29
21	21101	42	F	A	—	—	Normal. Size: 100 × 100 mm.	30
22	1501	66	M	A	—	—	n.d. Size: 60 × 60 mm.	19
23	20501	40	F	O	—	—	n.d. Minute cancer associated with adenomatous goiter.	31
24	20201	45	M	Lat (pap)	(Case with quintuple ca.)	—	n.d. Size: ca. 15 × 10 mm. Gastric cancer in WS father (age 37 yrs).	32
25	1901	45	M	Lat (pap)	MDS (44)	—	Scarlike cancer in atrophic thyroid. Size: 15 × 11 × 11 mm.	33
26	21701	62	M	Lat	MDS (60), meningioma (59)	—	n.d. Size: n.d.	34

Mean age 38.7 (n = 23) F:M = 16:7

Histology of thyroid carcinoma: F, follicular; P, papillary; A, anaplastic; O, other; Lat, latent carcinoma; Lat (pap), latent carcinoma, papillary subtype. Tumors in other organs: OS, osteosarcoma; MFH, malignant fibrous histiocytoma; AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; SqCC, squamous cell carcinoma; n.d., thyroid function not described. p.c., personal communication.

^a The thyroid tumor contained a mixture of follicular and clear cells.

^b Normal range of thyroglobulin, 10–40 ng/mL.

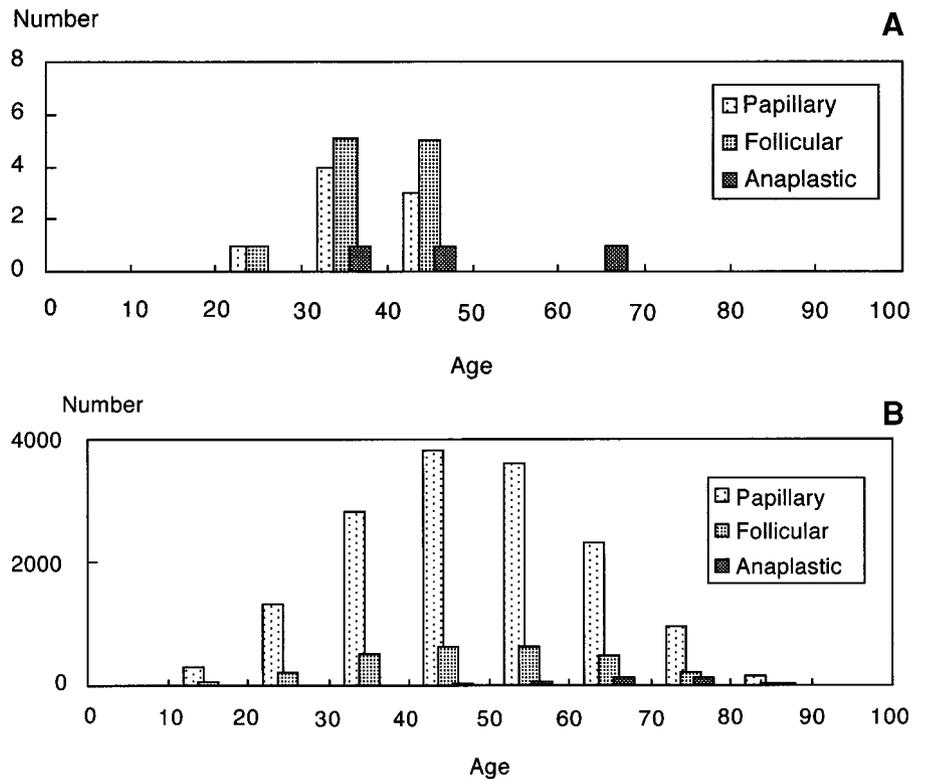


FIGURE 1. (A) Frequency distribution of thyroid carcinomas in Japanese patients with Werner syndrome is shown by age ($n = 24$). (B) Frequency distribution of thyroid carcinomas in the general Japanese population is shown by age ($n = 19,446$).

such as those of the lung, colon, or prostate, seldom occurred. The ratio of epithelial to nonepithelial cancer was 1:1 instead of the usual 10:1 in populations older than 20 years.⁶ We report here unusual features of 23 thyroid carcinomas in Japanese with WS in terms of clinicopathology, molecular genetics, and epidemiology, as compared with the general Japanese population.

MATERIALS AND METHODS

Our WS tumor file contained 185 neoplasms among 845 WS patients from the period 1966–1996, ascertained from case reports, personal communications, and patients examined by one of the authors (M.G.). The diagnosis of WS was based on the presence of three of four criteria: unusual body habitus (short stature and stocky trunk with spindly limbs), premature senescence (gray hair, cataracts, osteoporosis, and arteriosclerosis), scleroderma-like skin changes, and endocrine disorders (diabetes mellitus or hypogonadism).⁷ Pathologic diagnosis of thyroid tumors was as given by the original authors, mainly based on the Japanese criteria,⁸ which are largely according to the World Health Organization histologic classifications.⁹ Comparison was made with data from a Japanese nationwide registry of thyroid carcinoma (the Japanese National Thyroid Cancer Registry, 19,446

cases, 1977–1991).¹⁰ Germline mutations of WRN were examined in peripheral blood samples from six patients by methods previously described.^{11,12} Each mutation was referred to as previously designated by Yu et al.⁴ for mutations 1–4, by Goto et al.¹² for mutation 5, and by Matsumoto et al.⁷ for mutations 6–10. The study regarding mutation analysis using patients' blood was approved by our institutional review board, and informed consent was obtained from the patients.

RESULTS

Of 150 cancers, 26 were thyroid carcinomas (Table 1). Twenty-three were diagnosed during life and three (excluded from the analysis) were found incidentally at autopsy.

Age, Gender, and Histology

The mean ages (\pm standard deviation) for the WS patients was 38.7 years (± 7.4 , range 27–60), 10 years younger than the mean age of thyroid carcinoma patients in the general Japanese population (48.8 ± 14.7 , $P < 0.0005$) (Table 1). The age distributions were similar for papillary and follicular carcinomas among Japanese with WS; almost all cases occurred at ages 30–49 years (Fig. 1A) as compared with bell-shaped frequencies by age for the general Japanese population, with peaks at ages 40–59 years (Fig. 1B).

TABLE 2
Comparisons of Female-to-Male Ratios of Thyroid Carcinoma Patients among Japanese with Werner Syndrome and in the General Japanese Population (from the Japanese National Thyroid Cancer Registry), by Histology

	Werner syndrome		General Japanese population	
	No. of cases (%)	Ratio (F/M) (No. of cases)	No. of cases (%)	Ratio (F/M) (No. of cases)
Papillary carcinoma	8 (35)	3.0:1 (6:2)	15193 (78)	6.6:1 (13,194:1999)
Follicular carcinoma	11 (48)	2.7:1 (8:3)	2720 (14)	5.9:1 (2326:394)
Anaplastic carcinoma	3 (13)	0.5:1 (1:2)	377 (2)	2.3:1 (264:113)
Other	1 (4)	— (1:0)	1150 (6)	3.7:1 (905:245)
Total	23 (100)	2.3:1 (16:7) ^a	19440 (100)	6.1:1 (16,689:2751) ^a

^a The difference of the ratios is statistically significant ($P < 0.005$).

TABLE 3
Comparison of Distribution of WRN Mutations in Japanese with Werner Syndrome between Patients Developing Thyroid Carcinoma and All Patients Examined in Japan, Based on Our Own Studies

Mutation	a) In terms of patients		Mutation	b) In terms of alleles	
	No. of patients in all Japan (%)	No. of patients in thyroid series (%)		No. of mutated alleles in all patients (%)	No. of mutated alleles in thyroid series (%)
1/1	1 (1.1)		1	11 (6.3)	1 (8)
4/4	32 (36.8)	2 (33)	2	0 (0)	
5/5	1 (1.1)		3	0 (0)	
6/6	13 (14.9)	1 (17)	4	83 (47.7)	5 (42)
7/7	1 (1.1)	1 (17)	5	2 (1.1)	
8/8	1 (1.1)		6	31 (17.8)	2 (17)
9/9	1 (1.1)		7	2 (1.1)	2 (17)
10/10	1 (1.1)		8	2 (1.1)	
1/4	6 (6.9)	1 (17)	9	2 (1.1)	
4/6	4 (4.6)		10	2 (1.1)	
1/?	3 (3.4)		?	39 (24.4)	2 (17)
4/?	9 (10.3)		Total	174 (100.0)	12 (100)
6/?	1 (1.1)				
?/?	13 (14.9)	1 (17)			
Total	87 (100.0)	6 (100)			

The female-to-male ratio for WS patients with cancer was 2.3 to 1, versus 6.1 to 1 in the general Japanese population. Table 2 shows no differences in gender ratio (F/M) for follicular versus papillary cell type in WS patients (approximately 3 to 1) or in the general Japanese population (approximately 6 to 1). Of thyroid carcinomas in WS patients, 8 of 23 (35%) were diagnosed as papillary carcinomas, as compared with 15,193 of 19,440 (78.2%) in the Japanese National Thyroid Cancer Registry ($P < 0.005$).

Multiple or Familial Tumors

The occurrence of multiple tumors in WS is relatively common (Table 1). Among the 23 clinical cases of thyroid carcinoma in Japanese patients with WS, 7 had multiple primary cancers and 2 others had benign meningiomas. In addition, all three with thyroid car-

cinoma discovered postmortem had multiple tumors, five of them in one case. Two others had myelodysplastic syndrome (MDS), one of whom also had a benign meningioma.

The known familial occurrences of tumors were in brothers and in a father and his son, all of whom had WS: a brother of Case 21 developed glioblastoma of cerebellum and cystic adenoma of thyroid, and the father of Case 25 had WS and gastric carcinoma (Table 1). It is noteworthy that both Case 21 and his brother had thyroid tumors, though the brother's was benign, and both Case 25 and his father developed gastric adenocarcinomas.

Germline Mutations

Our studies of the mutations among Japanese with WS have been partly reported^{11,12} and all results for 87

TABLE 4
Werner Syndrome Gene (WRN) Mutations Reported in All Human Populations

No.	Site (nucleotide no.)	Codon	Type of mutation	Nucleotide sequence	Comments	Predicted protein
1	4144	1305	Substitution	CGA→TGA	Nonsense	1304 a.a.
2	3724	1165	Substitution	CAG→TAG	Nonsense	1164 a.a.
3	2-bp upstream from 5' end of exon 32 and 3919–3920	1230	4-bp deletion	ctgtagACAGA→ctgtAGA	Frame shift	1392 a.a.
4	1-bp upstream from 5' end of exon 26	1047–1078	Substitution	aatagGGTAGA→aatacggtaga	Exon skip and frame shift	1060 a.a.
5	4146	1305	1-bp insertion	CGAGCA→CGAAGC	Frame shift	1317 a.a.
6	1336	369	Substitution	CGA→TGA	Nonsense	368 a.a.
7	3677	1149	1-bp deletion	GAGCAG→GGCAGG	Frame shift	1160 a.a.
8	7-bp upstream from 5' end of exon 30 (3690–3691)	1153–1154	Substitution	ttgttcagATT→ttagTTCAGATT	Frame shift	1162 a.a.
9	1620	463	Substitution	TAT→TAA	Nonsense	462 a.a.
10	733–734	168	2-bp deletion	AAGCTG→GCTGAA	Frame shift	176 a.a.
11	3541–3614	1104–	74-bp deletion	Exon 28 deletion	Frame shift	1138 a.a.
12	1396	389	1-bp deletion	GAAAGA→GAAGAC	Frame shift	391 a.a.
13	3691–3803	1154–	113-bp deletion	Exon 30 deletion	Genomic deletion	1157 a.a.
14	1509	426	4-bp insertion	ATCA insertion	Frame shift	429 a.a.
15	Intron (2319–2320)	696–697	105-bp insertion		Nonsense in inserted DNA	708 a.a.
16 ^a	2320–3056	697–942	>1 kb deletion	Exons 19–23 deletion	Genomic deletion	704 a.a.
17	2896	889	Substitution	CGA→TGA	Nonsense	888 a.a.
18		816–817	Substitution	CAGgtatga→CAGTTATGA	At splice donor site	817 a.a.
19 ^a		697–942	Deletion	Exons 19–23 deletion	Genomic deletion	1186 a.a.

Details of mutations no. 1–4 were based on Yu et al.,⁴ no. 5 on Goto et al.,⁵ no. 6–10 on Matsumoto et al.,¹¹ no. 11–17 on Oshima et al.,³⁵ and no. 18,19 on Yu et al.³⁶

^a Mutations 16 and 19 were considered different.

marked in WS (in adults). Other cancer predisposition in WS is to nonepithelial neoplasia, whereas in BS it is to non-Hodgkin lymphoma in childhood and carcinomas in adulthood, primarily of the gastrointestinal tract. There is no excess of thyroid tumors in BS.

Ten mutations have thus far been identified in the WRN among 63 Japanese with WS.¹¹ The distribution of mutations in 87 patients, including newly identified ones, are compared with that for 6 patients with thyroid carcinomas. The mutations found in the thyroid carcinoma patients were typical of those found overall among Japanese patients with WS (Table 3), and thus it appeared that no particular mutations have a link to thyroid tumorigenesis. There is, however, a difference in *tumor spectrum* between Japanese and whites; in fact, no increase in the frequency of thyroid carcinoma has been found among whites, although they have increased frequencies of soft tissue sarcoma, osteosarcoma, and benign meningioma, as do the Japanese. Possibly the excess of thyroid tumors are due to environmental disparities, particularly a diet rich or

deficient in iodine. However, the *mutational spectrum* is different between Japanese and whites, as demonstrated in Table 5. A genotype–phenotype relation would be consistent with these findings. Possibly mutation 4 plays a key role in the genesis of thyroid carcinoma in WS patients; this is common in Japanese, but not in whites, with the syndrome. To our knowledge, whites have had only one clinical thyroid carcinoma reported, with no more information given than the diagnosis “struma maligna” and malignant epithelial tumor,⁴⁰ as well as an additional latent case with papillary carcinoma found at autopsy.⁴¹

As has been recently revealed, the nuclear localization signal (NLS) is near the C-terminal⁴² in the downstream of mutation 1 (Fig. 2). This finding raises the possibility that several mutations can cause the loss of NLS and lead to a similar phenotype. However, whether or not the defective protein of WRN includes the helicase domain may be important. The mutation of one papillary carcinoma studied here was in the N-terminal region, whereas those of the four follicular

TABLE 5A
Comparison of Distributions of WRN Mutations in Japanese and Whites with Werner Syndrome, Based on the Current Study and the Literature

Mutation no.	No. of mutated alleles (This study, Yu et al., ^{4,36} and Oshima et al. ³⁵)		Location
	Japanese	Whites	
1	19 (11+8+0+8 ^a)	2 (0+2+0+0)	C
2	2 (0+2+0+2 ^a)	4 (0+0+4+0)	C
3	0 (0+0+0+0)	8 (0+8+2 ^a +0)	C
4	119 (83+36+0+34 ^a)	0 (0+0+0+0)	C
5	2 (2+0+0+0)	0 (0+0+0+0)	C
6	36 (31+0+5+5 ^a)	11 (0+0+2+9)	N
7	4 (2+0+2+0)	0 (0+0+0+0)	C
8	2 (2+0+0+0)	0 (0+0+0+0)	C
9	2 (2+0+0+0)	0 (0+0+0+0)	N
10	2 (2+0+0+0)	0 (0+0+0+0)	N
11	1 (0+0+1+0)	0 (0+0+0+0)	C
12	0 (0+0+0+0)	2 (0+0+1+1)	N
13	0 (0+0+0+0)	1 (0+0+1+0)	C
14	0 (0+0+0+0)	2 (0+0+2+0)	N
15	0 (0+0+0+0)	2 (0+0+2+0)	HD
16	0 (0+0+0+0)	1 (0+0+1+0)	HD
17	0 (0+0+0+0)	4 (0+0+1+3)	C
18	2 (0+0+0+2)	0 (0+0+0+0)	HD
19	0 (0+0+0+0)	2 (0+0+0+2)	HD
Total	191	39	

C, the C-terminal region of WRN gene; N, the N-terminal region; HD, the helicase domain.
^a Omits cases that match others previously reported by Yu et al.⁴; 8 with mut 1; 2 with mut 2; 34 with mut 4; and 5 with mut 6 reported by Yu et al.³⁶ for Japanese; also 2 with mut 3 reported by Oshima et al.³⁵ for whites. For identification of each patient, the same abbreviations were principally regarded as the same patients, but SUG17802³⁵ was considered different from SUG1³⁶ because of different lengths of predicted proteins. (Therefore, mutations 16 and 19 were regarded as different.) All the patients presented for mutations 1–4 Yu et al.³⁶ were assumed to be contained in Yu et al.⁴

TABLE 5B
Distribution of WRN Mutations among Japanese as Compared with Whites by Different Locations of Mutations in WRN Gene Product, Based on the Data of Table 5A

	No. of mutated alleles	
	In Japanese (%)	In Whites (%)
N-terminal region	40 (21)	15 (38)
Helicase domain	2 (1)	5 (13)
C-terminal region	149 (78)	19 (49)
Total	191 (100)	39 (100)

carcinomas were in the C-terminal region (Fig. 2). As mutation 6 results in truncation of protein, the WRN protein of the papillary carcinoma, unlike those of the follicular carcinomas, does not contain the helicase domain. This suggests another possible genotype–phenotype relation with regard to the histology of thyroid carcinoma.

Follicular and papillary thyroid carcinomas have rarely been reported together with genetic traits: in familial adenomatous polyposis,⁴³ Cowden disease,⁴⁴ and in a few families as an autosomal dominant fashion.⁴⁵ Because patients with WS are at much higher risk for follicular or papillary thyroid carcinoma than any other group, they offer a special opportunity to study the pathogenesis of the neoplasm in this syndrome, perhaps as compared with other genetic disorders associated with lower risk.

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