Japan, the frequency of HB cases in Japan is too high to be explained only by publication bias. There may be some racial differences that promote HB and suppress WT in Japanese T18 cases.

Key words: Edwards syndrome; Hepatoblastoma; Japan; USA; Wilms tumor

© 2016 The Authors. Published by ACT Publishing Group Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Nishi M. Possible Japanese Racial Predisposition for Particular Tumors in Edwards Syndrome. Journal of Tumor 2016; 4(5-6): 456-460 Available from: URL: http://www.ghrnet.org/index.php/jt/article/view/1836

INTRODUCTION

Congenital chromosomal disorders are sometimes accompanied by malignant diseases. For example, it is well known that persons with Down syndrome have an increased risk of leukemia. Employing articles and abstracts, we reported a tumor profile in those with Edwards syndrome, or trisomy 18 (T18), and they are at high risk for several malignant tumors such as hepatoblastoma (HB) or Wilms tumor (WT), etc[1]. At the same time, however, it was noted that there were regional differences (Japan vs the USA) in the frequency of developing them.

The mortalities of adulthood malignancies (gastric cancer, breast cancer, etc.) are different between Japan and the USA[2]. These differences seem to be dependent mainly on the differences in lifestyle, but part of them might be attributable to racial factors. In this report, based on these articles and abstracts, the frequencies of HB in Japan and the USA are compared.

NUMBER OF CASES REPORTED

In this article, the same references employed in our previous article[3] are used. Using the key words “trisomy 18”, “malignancy”, “hepatoblastoma”, “Wilms tumor”, “leukemia”, “neuroblastoma”, and so on, articles and abstracts reporting patients with trisomy 18 and malignant neoplasms were gathered from “Pubmed” and
Then, why do Japanese T18 cases rarely develop WT? Are there any differences in the general incidences of WT? 

Table 1 Reported T18 cases with HB in Japan.

| Year | Author(first) | Karyotype | Sex |
|------|---------------|-----------|-----|
| 1983 | Ace           | 47XX+18   | F   |
| 1992 | Tanaka        | 47XX+18, 46XX | F |
| 1992 | Ariwa         | 47XX+18   | F   |
| 1997 | Tamada        | 47XX+18   | F   |
| 2001 | Maruyama      | 47XX+18   | F   |
| 2004 | Takahashi     | 47XX+18, 46XX | F |
| 2012 | Jekusa        | 47XY+18   | M   |

Table 2 Reported T18 cases with leukemia or WT in Japan.

| Year | Author(first) | Karyotype | Sex | Malignancy |
|------|---------------|-----------|-----|------------|
| 2005 | Tateishi      | 47XX+18   | F   | leukemia   |
| 1992 | Suzuki, Y     | 47XY+18   | M   | WT         |

Table 3 Reported T18 cases with HB in the USA (journal articles).

| Year | Author(first) | Karyotype | Sex |
|------|---------------|-----------|-----|
| 1987 | Dasouski      | 47XX+18   | F   |
| 1989 | Mamlok        | 47XX+18   | F   |
| 1996 | Bove          | 47XX+18   | F   |
| 2011 | Fernandez     | 47XY+18, 46XY | M |
| 2012 | Pereira       | 47XX+18, 46XX | F |

Table 4 Reported T18 cases with WT in the USA (journal articles).

| Year | Author(first) | Karyotype | Sex |
|------|---------------|-----------|-----|
| 1969 | Geiser        | 47XX+18   | M   |
| 1981 | Karayalcin   | 47XY+18   | F   |
| 1990 | Sheng         | 47XX+18   | M   |
| 1995 | Olson         | 47XX+18   | F   |
| 2003 | Anderson      | 47XX+18   | F   |

Table 5 Number of HB and WT in the T18 cases.

| Region | HB | WT |
|--------|----|----|
| Japan  | 21(7°) | 0(0°) |
| USA    | 7 | 8 |

**FACTORS SHOWING NO LARGE DIFFERENCE BETWEEN THE CASES OF JAPAN AND THE USA**

The distribution of age at diagnosis of both groups is similar. Most of them were discovered at 0 or 1 year of age (18 out of the 21 cases in Japan and 3/5 in the USA; Table 6, p > 0.10, chi-square test).

In the HB cases of Japan and those of the USA, there are several factors showing no large difference. There are more female cases both in Japan (17/21) and in the USA (4/5) (Table 7; p > 0.10, chi-square test).

There are only a small number of cases whose clinical stage of HB was confirmed, but no large difference was found in this, either (Table 8).

**GENERAL SURVIVAL RATES OF PATIENTS WITH T18**

What are the general survival rates of patients with T18? Several authors have reported them and, evidently, the 1-year-survival rates for Japanese (6-25%;)[3-15] are longer than those for westerners (4-8%)[16-20] (Table 9). Six-month-survival rates of Japanese cases are longer, too (12-50% vs 5-9%; Table 10). One-month-survival rates for Japanese (6-25%) are longer than those for westerners (4-11%). There may be a tendency for many patients with T18 in western countries to die within a short period of time after their birth.

**INFANT MORTALITY**

There is a difference in infant mortality between Japan and the USA. The present infant mortality of Japan is the lowest in the world (2.3 per 1,000 live births), being less than half of that of the USA (6.1)[21] (Table 12). This might lead to the high survival rates of patients with T18, and long survival leads to increased chances to develop HB. That is, the low infant mortality rate might be one of the factors that explain why HB is frequent in Japanese T18 cases.

**WILMS TUMOR**

Then, why do Japanese T18 cases rarely develop WT? Are there any differences in the general incidences of WT?
Hokkaido Prefecture is the northernmost main island of Japan. Since 1969, a nationwide program of childhood cancer registration (the Japan Children’s Cancer Registry) has been conducted[56]. The Hokkaido Children’s Cancer Registry is its branch. The registration rate in Hokkaido is at least 90% because there are only 5 hospitals that can treat children’s malignancies there, and therefore registration can be done with ease. On the other hand, the rate of the Japan Children’s Cancer Registry is about 40-50%. According to the Japan Children’s Cancer Registry, from 1969 to 2014, only 5 T18 cases were registered, and all of them had HB.

The incidence of WT in Hokkaido is about 3.1 (0-14 years of age, 1969-2012, per million). But that in the USA is 7.6[57]. Therefore, its ratio is about 1: 0.25 (the USA: Japan). If there is no difference in incidence of a tumor between the 2 countries, its number in Japan is a quarter of that in the USA. Since the number of the cases with WT in Japan is 1, the expected number of the cases in the USA is 4. Because its observed number in the USA is 8, its chi-square value is 4 ($p < 0.01$). Therefore, there is a large difference in the incidence of WT between Japan and the USA (Table 13). This difference might partly explain why there are a small number of cases with WT in T18 in Japan.

### Statistical estimation based on the number of live births

However, differences in survival rates of those with HB or the general incidences of WT cannot be the final explanation. In the USA, the number of live births in 2012 was 3,952,841 and that of Japan in 2013 was 1,029,816[58]. Therefore, its ratio is about 1: 0.25 (the USA: Japan). If there is no difference in incidence of a tumor between the 2 countries, its number in Japan is a quarter of that in the USA. Since the number of the cases with WT in Japan is 1, the expected number of the cases in the USA is 4. Because its observed number in the USA is 8, its chi-square value is 4 ($p < 0.05$). On the other hand, the expected number of the cases with HB in Japan is 1.25, since the number of the cases in the USA is 5.Since the observed numbers in Japan are 7 (journal articles only) and 21 (total), its chi-square values are 26.45 ($p < 0.01$) and 312.05 ($p < 0.01$), respectively. Thus, in any case, the number of cases with HB in Japan is significantly large. In addition, Matsuoka[59] reported that out of 43 autopsied cases with T18, 3 ones had HB. There are likely to be some racial differences in the case of T18. For example, genes in Japanese patients with T18 might promote HB and suppress WT.

According to the previous reports concerning the tumor profile in Down’s syndrome (0-14 years of age), leukemia constituted 93% (27 cases out of 29) in Japan[60], and 97% (31/32) in Denmark[61]. This difference is small, which brings out the high incidence of cases with HB in T18 in Japan.

### CONCLUSIONS

Between Japan and the USA, there are no large differences in the characteristics (age, sex and clinical stage) of T18 cases with HB. But the differences in frequency of HB and WT between Japan and the USA are too large to be explained only by publication bias. There

---

**Table 6** Age at diagnosis of HB in the T18 cases.

| Age (year) | Japan | USA |
|-----------|-------|-----|
| 0         | 6     | 2   |
| 1         | 5     | 3   |
| 2         | 2     | 1   |
| 10        | 3     | 1   |
| Unknown   | 3     | 1   |
| Total     | 21    | 9   |

**Table 7** Number of males and females in the T18 cases with HB.

| Sex     | Japan | USA |
|---------|-------|-----|
| Male    | 2     | 1   |
| Female  | 37    | 4   |
| Unknown | 5     | 1   |

**Table 8** Clinical stage of HB in the T18 cases.

| Stage | Japan | USA |
|-------|-------|-----|
| I     | 5     | 2   |
| II    | 1     | 3   |
| III   | 1     | 3   |
| IV    | 1     | 1   |

**Table 9** 1-year-survival rates of T18.

| Author(first) | Area     | Period | | rate |
|---------------|----------|--------|---|------|
| Kosho         | Nagano   | 1994-2003 | 24 | 25%  |
| Kondo         | Nagoya   | 2000-2009 | 17 | 19%  |
| Imataka       | Japan    | 1997-2003 | 19 | 9%   |
| Iwami         | Osaka    | 1994-2004 | 16 | 8%   |
| Iwami         | Osaka    | 2004-2009 | 12 | 7%   |
| Western countries |         |        |    |      |
| Rasmussen     | Atlanta  | 1968-1999 | 114 | 8%   |
| Root          | Utah     | 1979-1988 | 54 | 5%   |
| Carter        | Queensland | 1985 | 43 | 4%   |

**Table 10** 6-month-survival rates of T18.

| Author(first) | Area     | Period | | rate |
|---------------|----------|--------|---|------|
| Imataka       | Japan    | 1997-2003 | 17 | 18%  |
| Iwami         | Osaka    | 1994-2004 | 18 | 18%  |
| Iwami         | Osaka    | 2004-2009 | 12 | 12%  |
| Western countries |        |        |    |      |
| Root          | Utah     | 1979-1988 | 14 | 7%   |
| Carter        | Queensland | 1985 | 13 | 4%   |

**Table 11** 1-month-survival rates of T18.

| Author(first) | Area     | Period | | rate |
|---------------|----------|--------|---|------|
| Kosho         | Nagano   | 1994-2003 | 24 | 83%  |
| Kondo         | Nagoya   | 2000-2009 | 17 | 57%  |
| Imataka       | Japan    | 1997-2003 | 19 | 64%  |
| Iwami         | Osaka    | 1994-2004 | 18 | 39%  |
| Iwami         | Osaka    | 2004-2009 | 12 | 83%  |
| Western countries |        |        |    |      |
| Rasmussen     | Atlanta  | 1968-1999 | 14 | 9%   |
may be some racial differences that promote HB and suppress WT in Japanese T18 cases.

ACKNOWLEDGMENTS
I deeply thank Dr. Daniel Satgé for his useful advice.

REFERENCES
1 Satgé D, Nishi M, Sivrent N, Vekemans M. A tumor profile in Edwards syndrome (trisomy 18). *Am J Med Genet Part C Semin Med Genet* 2016; 999C: 1-11. [DOI: 10.1002/ajmg.c.31511. Epub 2016 Jul 30]

2 Nishi M. Lifestyle and cancer after the Second World War in Japan. [doi: 10.6051/j.isss.1819-6187.2014.02.48]

3 Abe T, Tanaka H, Tokunaga A, Jou H, Saitou K, Nishida K. Autopsy of hepatoblastoma with trisomy 18. *J Pediatr Practice* 1993; 46: 499. [1983191367 (http://search.jamas.or.jp/index.php)]

4 Tanaka K, Uemoto S, Asonuma K, Katayama T, Utsunomiya H, Akiyama Y, Sasaki MS, Ozawa K. Hepatoblastoma in a 2-year-old girl with trisomy 18. *Eur J Pediatr Surg* 1992; 2: 298-300. [PMID: 133994; DOI: 10.1055/s-2008-1063464]

5 Arika R, Eguchi H, Sugaya A, Takikawa I, Akiyama K, Imura S, Ishihara M. Large hepatoblastoma in a girl with trisomy 18. *Jpn J Pediatr Oncol* 1992; 29: 373-375. [1993238941 (http://search.jamas.or.jp/index.php)]

6 Hamada Y, Iiyama H, Koshiji M, Sato M, Koga T, Tatsumi K, Teraguchi M, Sakaida N, Okamura A, Hiki K. Multiple hepatoblastomas associated with trisomy 18 ---report of a case---. *J Jpn Pediatr Soc* 1997; 43: 302-305. [PMID: 11380930]

7 Teraguchi M, Nogi S, Ogino H, Kawasaki H, Kohdera U, Kino M, Kobayashi Y, Koshiji M, Furukaka M, Hamada Y, Hiki K. Hepatoblastoma with trisomy 18. *Jpn J Pediatr Oncol* 1994; 31: 597. [1995185728 (http://search.jamas.or.jp/index.php)]

8 Teraguchi M, Nogi S, Ikemoto Y, Ogino H, Kohdera U, Sakaida N, Okumura A, Harada Y, Kobayashi Y. Multiple hepatoblastomas associated with trisomy 18 in a 3-year-old girl. *Hematol Pediatr Oncol* 1997; 14: 463-467. [PMID: 9267879]

9 Iiyama H, Hamada Y, Koshiji M, Tanano A, Tsuji M, Sato M, Hiki K. Hepatoblastoma associated with trisomy 18. *J Pediatr Oncol Surg* 1997; 33: 770-775. [1998004710 (http://search.jamas.or.jp/index.php)]

10 Maruyama K, Ikeda H, Koizumi T. Hepatoblastoma associated with trisomy 18. *J Jpn Pediatr Soc* 2001; 98: 670. [2000191003 (http://search.jamas.or.jp/index.php)]

11 Takagki T, Misawa K, Takano T, Sato E, Aoki I, Oookubo H, Ishige K, Yuki K, Shimizu Y, Oonishi K. Hepatoblastoma with trisomy 18 treated by surgical operation. *Shinshu Med J* 2004; 52: 296. [2004300554 (http://search.jamas.or.jp/index.php)]

12 Ito K, Saito M, Chiba H, Takahashi R, Yamada Y, Nakae N. Hepatoblastoma in a very low birth weight infant with trisomy 18. *Jpn J Pediatr Oncol* 2004; 108: 272. [2004151799 (http://search.jamas.or.jp/index.php)]

13 Watanabe M, Shimada H, Shimazaki N, Takahashi T. Trisomy 18 with a severe congenital heart disease and hepatoblastoma. *Jpn J Pediatr Hematol* 2006; 20: 420. [2007102972 (http://search.jamas.or.jp/index.php)]

14 Nishi E, Nishi Y, Kawaguchi A, Yura K, Nishida Y, Watanabe S, Baba K. Hepatoblastoma in a female case with trisomy 18 treated by chemotherapy. *J Jpn Soc Perinit Neonat Med* 2006; 42: 417. [2006315589 (http://search.jamas.or.jp/index.php)]

15 Ohashi H, Goto T, Oomori Y, Sasaki N, Ogawa M, Fujitawara T, Higashikawa M, Inoue M. Hepatoblastoma with trisomy 18. *J Jpn Pediatr Soc* 2012; 116: 1399. [2013033931 (http://search.jamas.or.jp/index.php)]

16 Ogawa M, Ohashi H, Goto T, Oomori Y, Sasaki N, Fujitawara T, Higashikawa M, Inoue M. Hepatoblastoma with trisomy 18. *Jpn J Pediatr Hematol* 2006; 20: 340. [2007102814 (http://search.jamas.or.jp/index.php)]

17 Ishibashi H, Sogami T, Oshio T. Hepatoblastoma in 2 cases with trisomy 18. *J Jpn Soc Pediatr Surg* 2009; 45: 623. [2009224828 (http://search.jamas.or.jp/index.php)]

18 Ishibashi H, Oshio T, Sogami T. Hepatoblastoma with bile duct anomalies in a case with trisomy 18. *Jpn J Pediatr Oncol*. 2010; 47: 146. [2010163302 (http://search.jamas.or.jp/index.php)]

19 Kumikata T, Tamura M, Sobajima H, Suzuki K, Ezaki S, Takayama C, Ishiguro A, Ito T, Hoshi R, Kurishima K. Hepatoblastoma in a very low birth weight infant with trisomy 18. *J Jpn Soc Prenat Neonat Med* 2009; 21: 670. [2010060004 (http://search.jamas.or.jp/index.php)]

20 Sugitate R, Matsuyama Y, Shimizu N, Goto M, Terakawa T, Yoshihashi H, Komori H, Hirose S, Hasegawa Y. A case with trisomy 18 cured with surgical resection for hepatoblastoma. *Jpn J Pediatr Soc* 2012; 116: 325. [2012220040 (http://search.jamas.or.jp/index.php)]

21 Tateishi Y, Yasuda H, Ukae S, Oda T. A case of xantholeukemia
with trisomy 18 and café-au-lait spots. *Jpn J Dermatol* 2005; 115: 1181-1187. [PMID: 16060431]

Suzuki Y, Hino Y, Shibuya H, Hanamizu K, Noro T, Yoshinari M, Sato A, Suwabe N, Koizumi Y, Imazumi M, Tada K, Miura T, Watanabe H, Murakami K. A case with trisomy 18 mosaicism who had an orbital relapse of Wilms tumor after about 7 years. *Jpn J Pediatr Oncol* 1992; 29: 766. [PMID: 1993125949 (http://search.jamasis.or.jp/index.php)]

Dasouski M, Barr M. Trisomy 18 and hepatic neoplasia. *Am J Med Gen* 1987; 27: 203-205. [PMID: 3037903; DOI: 10.1002/ajmg.1320270122]

Mamlok V, Nichols M, Lockhart L, Mamlok R. Trisomy 18 and hepatoblastoma. *Am J Med Gen* 1989; 33: 125-126. [PMID: 2546426; DOI: 10.1002/ajmg.1320330119]

Bove KE, Soukup S, Ballard ET, Ryckman F. Hepatoblastoma in a child with trisomy 18: Cytogenetics, liver anomalies, and literature review. *Pediatr Pathol Labor Med* 1996; 16: 253-262. [PMID: 9025831]

Fernandez KS, Baum R, Fung B, Yeager N, Leonis MA, Wagner LM, Tiao G, Ross ME. Chromosomal hepatoblastoma in a patient with mosaic trisomy 18 treated with orthotopic liver transplantation. *Pediatr Blood Cancer* 2011; 56: 498-500. [PMID: 21113936; DOI: 10.1002/pbc.22768]

Pereira EM, Marion R, Ramesh KH, Kim JS, Ewart M, Ricafort R. Hepatoblastoma in a mosaic trisomy 18 patient. *J Pediatr Hematol Oncol* 2012; 34: e145-e148. [PMID: 22469941; DOI: 10.1097/MPH.0b013e3182459e88]

Geiser CF, Schindler AM. Long survival in a male with 18-trisomy syndrome and Wilms’ tumor. *Pediatr* 1969; 44: 111-116. [PMID: 4307567]

Geiser CF. Long survival in a male with 18-trisomy syndrome and Wilms’ tumor: A subsequent report. *Pediatr* 1973; 51: 153. [PMID: 4346229]

Karayalcin G, Shanske A, Honigman R. Wilms’ tumor in a 13-year-old girl with trisomy 18. *Am J Dis Child* 1981; 135: 665-667. [PMID: 6264780]

Sheng WW, Soukup S, Bove K. Chromosome analysis of 31 Wilms’ tumors. *Cancer Res* 1990; 50: 2786-2793. [PMID: 2158398]

Olson JM, Hamilton A, Breslow NE. Non-11p constitutional abnormalities in Wilms’ tumor patients. *Med Pediatr Oncol* 1995; 24: 305-309. [PMID: 7700182]

Anderson CE, Punnett HH, Huff V, de Chadarevian JP. Characterization of a Wilms Tumor in a 9-year-old girl with trisomy 18. *Am J Med Gen* 2003; 121A: 52-55. [PMID: 12900902; DOI: 10.1002/ajmg.a.20141]

Kitanovski L, Ovcak Z, Jazbec J. Multifocal hepatoblastoma in a 6-month-old girl with trisomy 18: a case report. *J Med Case Rep* 2009; 3: 8319. [PMID: 19830224; PMCID: PMC2726543; DOI: 10.4076/1752-1947-3-8319]

Suzuki Y, Hino Y, Shibuya H, Hanamizu K, Noro T, Yoshinari M, Sato A, Suwabe N, Koizumi Y, Imazumi M, Tada K, Miura T, Watanabe H, Murakami K. A case with trisomy 18 mosaicism who had an orbital relapse of Wilms tumor after about 7 years. *Jpn J Pediatr Oncol* 1992; 29: 766. [PMID: 1993125949 (http://search.jamasis.or.jp/index.php)]