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Title: Prevalence and Risk Factors of Carpal Tunnel Syndrome in Japanese Aged 50 to 89 Years

Running Title: Prevalence and Risk of Carpal Tunnel Syndrome

Keywords: Carpal tunnel syndrome, Prevalence, Epidemiology, Risk factor, Random sampling

Abstract:
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Methods: Subjects aged between 50 and 89 years were randomly sampled from the basic resident registry of a rural Japanese town. Subjects indicating a history of CTS surgery in a written questionnaire were classified as having past CTS. Subjects with both sensory disturbance of the median nerve area and delays in NCSs were diagnosed as having present CTS. Subjects with past or present CTS were judged as affected with CTS. We calculated the prevalence of CTS and investigated for possible risk factors.
Results: Seventeen subjects (14 female and 3 male) were affected with CTS among 379 enrolled subjects. Adjusting these results to Japanese population values, the weighted prevalence of CTS was 4.7% (female: 7.2%, male: 1.8%) in the Japanese population aged 50 to 89 years. Statistically significant positive correlations were found between CTS and female, higher BMI, rheumatoid arthritis, and trigger digit. In females affected with CTS, third metacarpal length was significantly shorter than in those without CTS.
Conclusions: This epidemiological study clarified the prevalence of CTS among Japanese seniors as 4.7%. Female, higher BMI, rheumatoid arthritis, trigger digit, and shorter third metacarpal length in females were risk factors for CTS.

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Text

INTRODUCTION

Carpal tunnel syndrome (CTS) is the most common entrapment neuropathy worldwide.[1,2] Conservative treatment and surgery are 60-75% and 69-95% effective, respectively, in improving clinical symptoms.[3-5] Prolonged CTS may diminish hand function and mental health and lead to decreases in the workforce and labor productivity; this socioeconomic loss was calculated as more than 2 billion dollars yearly in the United States.[6]

The prevalence of CTS has been reported to be 1-16% in Europe and the United States.[7-12] However, there are few studies on CTS prevalence from Asia.[13] The risk factors for CTS differ among previous reports and include female,[5,9,12,14-18] obesity,[17,19,20] diabetes mellitus (DM),[18-21] long-term hemodialysis treatment,[18] thyroid dysfunction,[17,18] rheumatoid arthritis (RA),[19] overuse of the hand,[8] use of vibratory tools,[8] and small hand size.[23]

The main purpose of this study was to clarify the prevalence of CTS diagnosed by both questionnaire of sensory disturbance of the median nerve area and NCSs in seniors randomly sampled from a Japanese rural town. We also aimed to calculate the prevalence of CTS among all Japanese seniors by adjusting the component ratios of age and gender between the town and the Japanese general population. Our third goal was to investigate for risk factors of CTS.

METHODS

The current study was one of a project in the "Obuse study", a cross-sectional Japanese cohort survey randomly sampled from a basic resident registry investigating the prevalence and risk factors of several aging disorders related to the bones, joint, spine, hands, and feet.[24] The town of Obuse is classified as a flat farming area[25] that is located in Nagano prefecture, Japan. With 11,326 inhabitants, the ratio of citizens older than 65 years of age was roughly one third in October 2014.[26]

Obuse public servants mailed information on the Obuse study cohort along with a request to enroll to residents between 50 and 89 years of age who were randomly selected from the town's population registry. We divided the subjects into 8 groups according to age (fifties, sixties, seventies, and eighties) and gender (male and female). Residents who agreed to participate in the study were collected until the number of subjects reached approximately 50 in each group. Consequently, 1,297 inhabitants aged 50-89 years randomly sampled from 5,352 individuals received request letters, with 415 participating. We excluded 34 participants with a history of wrist fracture and 2 participants with incomplete data, leaving 379 subjects registered in the final cohort for this CTS study (Figure 1).

Before their scheduled medical examination, we sent the subjects a questionnaire booklet asking them to describe their history and present status of life, drinking habits, smoking habits, medical conditions, mentality, and job. We extracted the questions related to

CTS (Figure 2) as well as those concerning smoking history (packs/year × number of years smoked), present drinking habits (grams of ethanol/day), history of using a vibratory tool for work, and job history. Regarding drinking habits, subjects were asked about the type of alcohol, amount consumed, and frequency of drinking per week by a questionnaire. We calculated the amount of ethanol intake per day from the obtained data. The grams of ethanol for each type of alcohol were considered as follows: 180 mL of rice wine contained 23 grams of ethanol, 180 mL of white spirits contained 36 grams of ethanol, 30 mL of whiskey contained 10 grams of ethanol, 60 mL of wine contained 6 grams of ethanol, and 633 mL of beer contained 23 grams of ethanol.[27] Concerning job history, we defined heavy manual laborers as subjects responding to have carried weights of over 10 kg at least 11 times/week for at least 10 years (Figure 3).

The subjects brought the questionnaire booklet to their medical examination. We verified the answers in each booklet and directly interviewed subjects if a response was unclear or left blank. Respondents who indicated both a history of diagnosis and surgery for CTS were defined as subjects with past CTS.

During the medical examination, we asked all enrolled subjects about any current numbness or tingling in the hands. If the case of yes, we asked them to indicate the areas of any numbness, tingling, or burning pain using hashed lines in a diagram (Figure 4) to classify subjects by sensory disturbance area into classic or probable CTS by Katz's criteria.[28] These

subjects were further investigated by NCSs of the bilateral median nerve. We measured motor distal latency (MDL) and sensory conduction velocity (SCV) across the wrist of the bilateral median nerve with a Neuropack μMEB-9104 (NIHON KODEN, Tokyo, Japan) according to Kimura's methods.[29] Individuals whose MDL surpassed 4.2 msec or whose SCV was delayed more than 45 m/sec were defined as having present CTS. Subjects with either past or present CTS were defined as subjects affected with CTS (Figure 5).

We calculated the prevalence of CTS among Japanese seniors as follows: the number of subjects with CTS was divided by number of enrolled subjects in each of the 8 groups classified by gender and age. We then multiplied this rate according to the Japanese population in each of the 8 groups. The 8 numbers were added and divided by the population of Japanese aged 50 to 89 years to estimate the national prevalence of CTS in this age group. Gender-based evaluations were performed using same calculation method.

All enrolled subjects were examined for anthropometric data, blood pressure, bone mineral density, and serological findings. We also collected information on gender, age, body height, body mass index (BMI), smoking amount, alcohol consumption, DM (HbA1c ≥ 6.5 mg/dl or past history of DM), past history of RA, thyroid dysfunction (past history of Basedow disease or hypothyroidism), and osteoporosis (T-score at proximal femur ≤ -2.5). Orthopedic physicians among the authors evaluated the subjects' hands directly. Trigger digit was diagnosed as a snapping phenomenon of the digit, tenderness of the skin over the A1

pulley, or a history of steroid injection or surgery for trigger digit. We measured third metacarpal length from plain posteroanterior radiographs of the hand as an index of hand size.[23)]

We divided the subjects into groups with and without CTS. Possible factors related to CTS (gender, age, BMI, smoking, alcohol, DM, dialysis, RA, thyroid dysfunction, osteoporosis, dementia, use of a vibratory tool, history of heavy manual labor, and trigger digit were all investigated. Univariate and multivariate logistic regression analyses were performed on demographic data and past history to identify factors related to CTS. Stepwise model selection based on Akaike's information criterion was applied to the results of multivariate analysis, and appropriate risk factors were selected. To investigate whether hand size was related to CTS, we performed univariate analysis between subjects with CTS and those without for third metacarpal length. All statistical analyses were performed with EZR software[30)] (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). The level of significance was set at $P < 0.05$.

The institutional review board of our institution approved this study prior to its commencement.

RESULTS

Among the 379 subjects enrolled, 6 were classified as having past CTS, with 3 and 3 possessing unilateral and bilateral afflictions, respectively. Seventeen subjects were judged as having classic or probable CTS according to indications on hand diagrams by Katz's criteria.[28] In these 17 subjects, 4 declined NCSs, leaving 13 subjects for further NCS evaluation. Seven of the 13 subjects had delayed MDL or SCV in bilateral median nerves and 4 had delayed MDL or SCV in a unilateral median nerve. Thus, 11 subjects (9 female and 2 male) had present CTS. Ultimately, 17 subjects (14 female and 3 male) were judged as affected with CTS. The total, female, and male prevalence of CTS were 4.5%, 7.4%, and 1.6%, respectively, among the rural town residents. Weighted values were based on the population composition ratio of Japan and represented the reference values for Japanese aged 50 to 89 years. Following gender and age adjustments, the total, female, and male prevalence of CTS in Japanese seniors aged 50 to 89 years were 4.7%, 7.2%, and 1.8%, respectively.

The demographics of subjects with or without CTS are shown in Table 1. Subjects with CTS included respective DM and history of trigger digit rates of > 20% (Table 2). Subjects with CTS had significantly larger proportions of female, higher BMI, RA, and trigger digit in univariate logistic analysis. In multivariate analysis, the significant findings of female, higher BMI, RA, and trigger digit all persisted. On the other hand, no significant relationships were observed for age, smoking, alcohol, DM, thyroid dysfunction, osteoporosis, use of a vibratory tool, or heavy manual labor (Table 3).

The mean ± standard deviation of third metacarpal length in the 14 female subjects with CTS was 56.6 ± 12.9 mm and significantly shorter than that in the 176 female subjects without CTS (58.8 ± 3.0 mm) (*t*-test, $P < 0.01$). The significance of a difference of third metacarpal length in males could not be determined due to insufficient statistical power.

DISCUSSION

The present study calculated the national prevalence of CTS as 7.2% in females and 1.8% in males among Japanese aged 50 to 89 years. Our methodology had several advantages. First, we selected the subjects randomly from the resident registry in of a rural town, thus reducing selection bias compared with a volunteer cohort study. Second, all enrolled subjects were examined for CTS risk factors by questionnaire, clinical findings by orthopedic physicians, blood examination, serological findings, bone mineral density, and radiography.

There are no gold standards for the diagnosis of CTS,[34-37] which is clinically identified by areas of numbness or tingling in the hand, clinical history, and positive Phalen test or Tinel sign.[38] In the current study, we initially used Katz's diagram for all subjects to diagnose CTS, and then examined subjects rated as having classic or probable CTS by NCSs. Katz's hand diagram is an easily administered and reproducible clinical tool, with classic or probable ratings yielding a sensitivity of 80% and specificity of 90% for CTS diagnosis.[28] Although NCSs have high a specificity for diagnosing CTS, normal NCS findings do not

160 necessarily rule out the condition.[36,39,40] Thus, the prevalence rate may have been
161 underestimated in this study because it excluded 4 subjects refusing NCSs and 2 subjects with
162 normal NCS findings.
163 Several previous studies on CTS prevalence employed hospital-based population
164 sampling.[12-16,31,32] Of the 4 prospective randomized population-based studies identified in a
165 PubMed search (Table 5), only 2 considered both clinical symptoms and NCSs.[7,8] in CTS
166 diagnosis. According to our calculations for subjects aged from 55 to 74 years in these 2
167 studies, the prevalence of CTS was 4.2% in Swedish females and 2.2% in Swedish males[8]
168 and 9.4% in Dutch females and 1.5% in Dutch males[7]. In the present investigation, the
169 weighted prevalence adjusted by Japanese national gender and age population values for ages
170 50 to 89 years was 7.2% in females and 1.8% in males. Thus, the prevalence of CTS in Japan
171 was very similar to those of the 2 European studies despite racial differences.
172 In earlier reports, female,[5,9,12,14-18] obesity or high BMI,[17,19,20] and RA[19] were risk
173 factors for CTS. The present study corroborated these findings. Trigger digit has been
174 nominated as a risk factor for CTS[33] by simple counting of CTS patients, but this possibility
175 has not been well examined. Our investigation identified trigger digit to be a risk factor for
176 CTS by a randomized sampling population-based study. Nakamichi and Tachibana[23]
177 observed that CTS was more likely to occur in small hands in their patient-based
178 retrospective study. In the present prospective study, shorter length of the third metacarpal

was a significant risk factor for female subjects with CTS; however, we could not confirm this in males due to a limited number of cases.

This study had several limitations. First, it did not include subjects in their twenties to forties who potentially had CTS. Second, of the 1,297 inhabitants receiving invitations to the Obuse study cohort, only 379 were finally enrolled in this CTS study, which could have introduced selection bias. Third, the number of enrolled subjects (379) was not a value calculated by power analysis, but rather one decided by resource availability.[24] Therefore, the analysis of risk factors may lack statistical power because the prevalence of CTS was low. Fourth, the subjects indicated a history of carpal tunnel release, wrist fracture, or injection for trigger digit based on their own understanding and memory, which potentially created recall bias. Fifth, subjects treated conservatively for CTS were overlooked since there were no questions regarding a history of conservative therapy. Sixth, the demographic and clinical findings obtained from a rural town cohort might not be directly applicable to those of the entire population.[24] Lastly, we could not differentiate subjects with diabetic neuropathy. Five of the 11 subjects with present CTS had DM and therefore possible diabetic neuropathy was included in these 5 subjects.

In spite of these limitations, the present study revealed the weighted prevalence of CTS as 7.2% in females and 1.8% in males in the Japanese general population aged from 50 to 89 years. Female, high BMI, RA, and trigger digit were risk factors for CTS. In females,

198 shorter length of the third metacarpal also constituted a risk for CTS.

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Table 1

Demographics of subjects with and without CTS

	All subjects (n=379)	Subjects with CTS (n=17)	Subjects without CTS (n=362)
Female / Male, number (%)	190 / 189	14 (7.4%) / 3 (1.6%)	176 (92.6%) / 186 (98.4%)
Age, years	69.4 (50–89)	71.5 (54–87)	69.3 (50–89)
BMI, kg/m^2	22.8 (14.8–35.8)	25.1 (18.1–35.8)	22.6 (14.8–31.8)
Smoking	4800 (0–28800)	3200 (0–51800)	4900 (0–51800)
Alcohol	12.1 (0–156.0)	7.0 (0–65.9)	12.4 (0–156.0)

Results are presented as the mean and range except for gender. CTS: carpal tunnel syndrome, BMI: body mass index, smoking: packs/year × number of years smoking, alcohol: grams of ethanol/day.

Table 2

Past and present conditions in the subjects

	All subjects (n=379)	Subjects with CTS (n=17)	Subjects without CTS (n=362)	P
Diabetes mellitus (DM)	54 (14.2%)	5 (29.4%)	49 (13.5%)	0.08
Hemodialysis	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Rheumatoid arthritis (RA)	9 (2.3%)	2 (11.8%)	7 (1.9%)	< 0.02*
Thyroid dysfunction	10 (2.6%)	1 (5.9%)	9 (2.5%)	0.41
Osteoporosis	22 (5.8%)	2 (11.8%)	20 (6.0%)	0.30
Use of vibrating tool	37 (9.8%)	1 (5.9%)	36 (9.9%)	0.59
Heavy manual labor	71 (18.7%)	3 (17.6%)	68 (18.8%)	0.90
Trigger digit (TD)	38 (10.0%)	6 (35.2%)	32 (8.8%)	< 0.01*

Results are presented as the number and rate in each group (%). CTS: carpal tunnel syndrome. * P < 0.05

Further analysis with a multivariate model is presented in Table 3.

Table 3

Impact of related factors on CTS

Candidate factor	Univariate analysis		Multivariate analysis	
	Odds ratio	P	Odds ratio	P
Demographics				
Gender (female)	4.9 (1.4–17.4)	< 0.05	3.8 (1.0–14.4)	< 0.05*
Age (+10 years)	1.2 (0.8– 1.8)	0.44		
BMI (+1 kg/m^2)	1.2 (1.1– 1.4)	< 0.01	1.3 (1.1– 1.5)	< 0.01*
Smoking (+100 packs/year × years)	1.0 (1.0– 1.0)	0.41		
Alcohol (+10 g ethanol/day)	1.0 (0.9– 1.0)	0.29		
Past and present conditions				
Diabetes mellitus	2.6 (0.9– 7.8)	0.08		
Rheumatoid arthritis	6.7 (1.3–35.1)	< 0.05	8.4 (1.4-51.9)	< 0.05*
Thyroid dysfunction	2.5 (0.3–20.5)	0.41		
Osteoporosis	2.3 (0.5–10.7)	0.30		
Use of vibratory tool	0.6 (0.1– 4.3)	0.59		
Heavy manual labor	0.9 (0.3– 3.3)	0.90		
Trigger digit	5.6 (2.0–16.2)	< 0.01	4.4 (1.4– 13.7)	< 0.05*

Odds ratios are presented with the 95% confidence interval. The results of multivariate analysis were selected after stepwise model selection. CTS: carpal tunnel syndrome, BMI: body mass index. * P < 0.05 in multivariate analysis

Table 4

Prevalence of CTS in previous prospective studies

Author	Country	Subject population	Diagnostic criteria	No. of subjects Total (Female/Male)	Age of subjects (years)	Prevalence of CTS Total (Female/Male)
De Krom MC, et al.[7]	Netherlands	Local government registry	Questionnaire and NCSs	504 (340/106)	25-74	(6.8%/0.6%)
Atroshi I, et al.[8]	Sweden	Local government registry	Clinical examination and NCSs	2466 (1134/1332)	25-74	2.7% (3.0%/2.1%)
Tanaka S, et al.[9]	United States	National health interview survey	Questionnaire	44233	18 or older	1.6% (1.9%/1.2%)
Shiri R, et al.[11]	Finland	National health examination survey	Clinical examination	6254 (2844/3410)	30 or older	(5.3%/2.1%)
Present Study	Japan	Local government registry	Questionnaire and NCSs	379 (190/189)	50-89	4.7% (7.2%/1.8%)*

CTS: carpal tunnel syndrome, NCSs: nerve conduction studies.

* Weighted prevalence adjusted by Japanese national gender and age population values for ages 50–89 years.

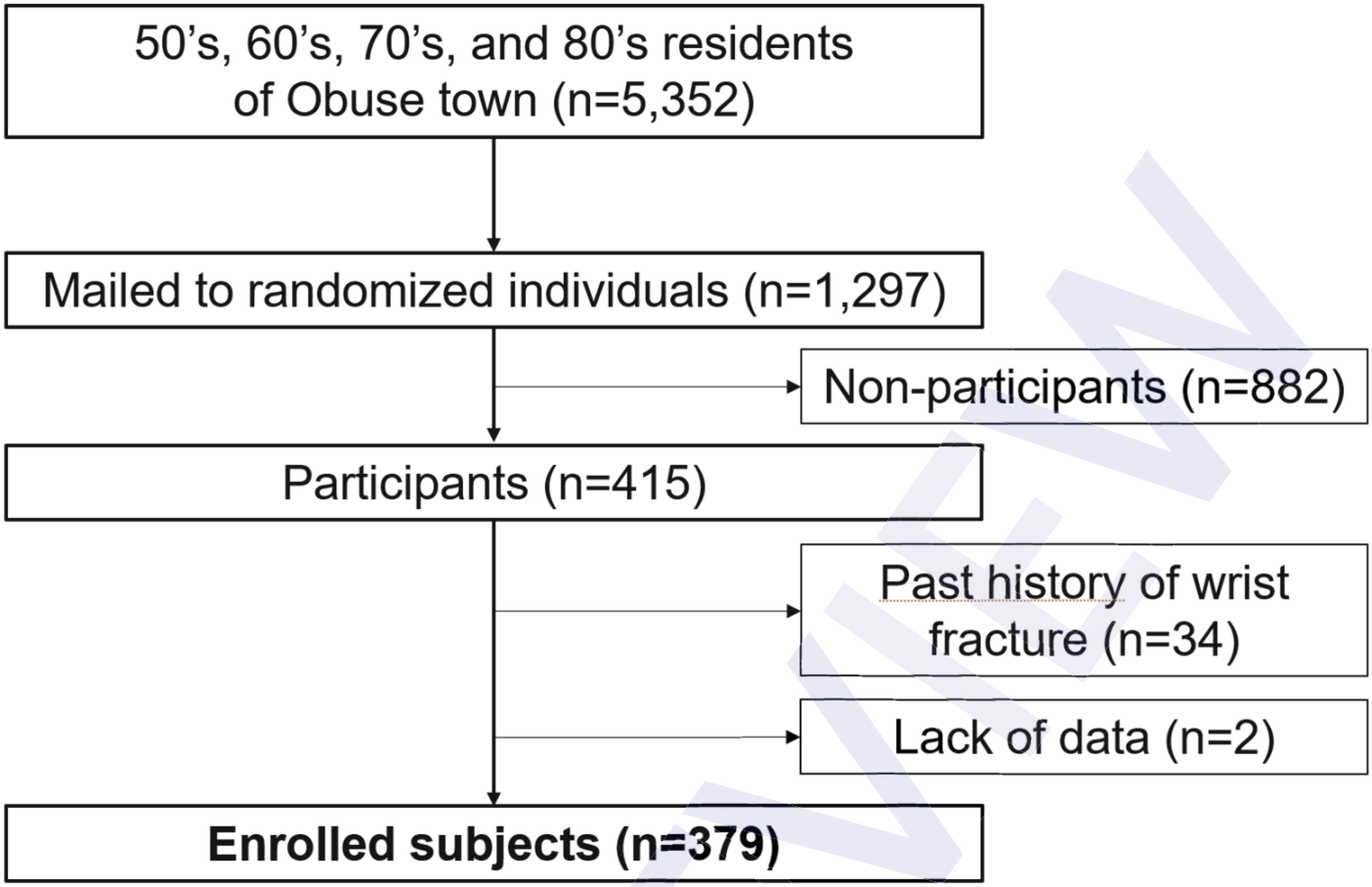


Fig. 1. Subject selection flowchart. A total of 1,297 inhabitants aged 50-89 years randomly sampled from 5,352 individuals received request letters, with 415 participating and 379 being registered in the study.

1) Have you ever been diagnosed as having a condition below?

☐ Trigger digit ☐ Carpal tunnel syndrome

☐ Cubital tunnel syndrome ☐ Rotator cuff tear ☐ Hallux valgus

2) At what age were you operated on for the conditions below, if applicable?

☐ Trigger digit __y ☐ Carpal tunnel syndrome __y

☐ Cubital tunnel syndrome __y ☐ Rotator cuff tear __y ☐ Hallux valgus __y

3) Have you ever broken a bone? ☐ Yes ☐ No

4) If you answered "yes" to the above question, please answer the following questions. In what region was the break?

☐ Upper arm ☐ Shoulder ☐ Wrist ☐ Digit ☐ Back ☐ Rib

☐ Lower leg ☐ Femur ☐ Knee/patella ☐ Ankle ☐ Other: _____

Fig. 2. Survey questions regarding carpal tunnel syndrome (CTS) and fractures. All subjects answered a questionnaire related to CTS and fractures. Respondents who indicated both a history of diagnosis and surgery for CTS were classified as having past CTS.

1) Please list all jobs you have ever done.

	Job position	Starting age	Quitting age
a.	_____	____ years old	____ years old
b.	_____	____ years old	____ years old
c.	_____	____ years old	____ years old
d.	_____	____ years old	____ years old
e.	_____	____ years old	____ years old

2) Approximately how often did you carry objects of over 10 kg in weight per week in your job history of a - e in the above question?

About job a:

☐None ☐Once/week ☐Twice to 10 times/week
☐At least 11 times/week ☐Cannot recall

About job b:

☐None ☐Once/week ☐Twice to 10 times/week
☐At least 11 times/week ☐Cannot recall

About job c:

☐None ☐Once/week ☐Twice to 10 times/week
☐At least 11 times/week ☐Cannot recall

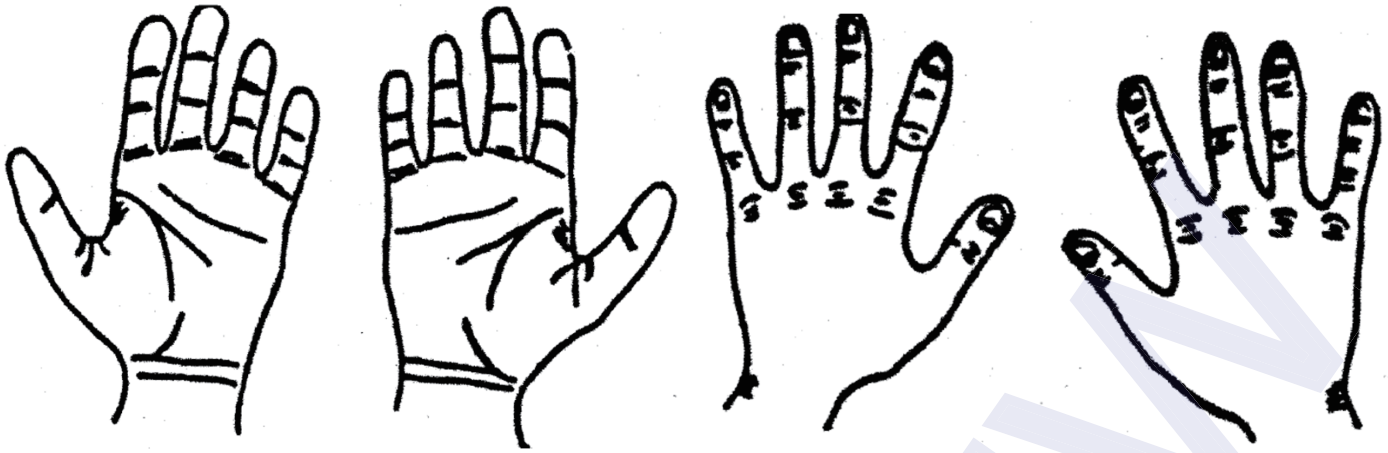
About job d:

☐None ☐Once/week ☐Twice to 10 times/week
☐At least 11 times/week ☐Cannot recall

About job e:

☐None ☐Once/week ☐Twice to 10 times/week
☐At least 11 times/week ☐Cannot recall

Fig. 3. Survey questions regarding job history. Heavy manual laborers were defined as subjects responding to have carried weights of over 10 kg at least 11 times/week for at least 10 years.



Please indicate using diagonal hashed lines any areas in which you presently feel numbness, tingling (like a prick), or burning pain.

Fig. 4. Drawing of hands used to indicate areas of numbness, tingling, or burning pain. We asked subjects to indicate such areas using hashed lines in the diagram.

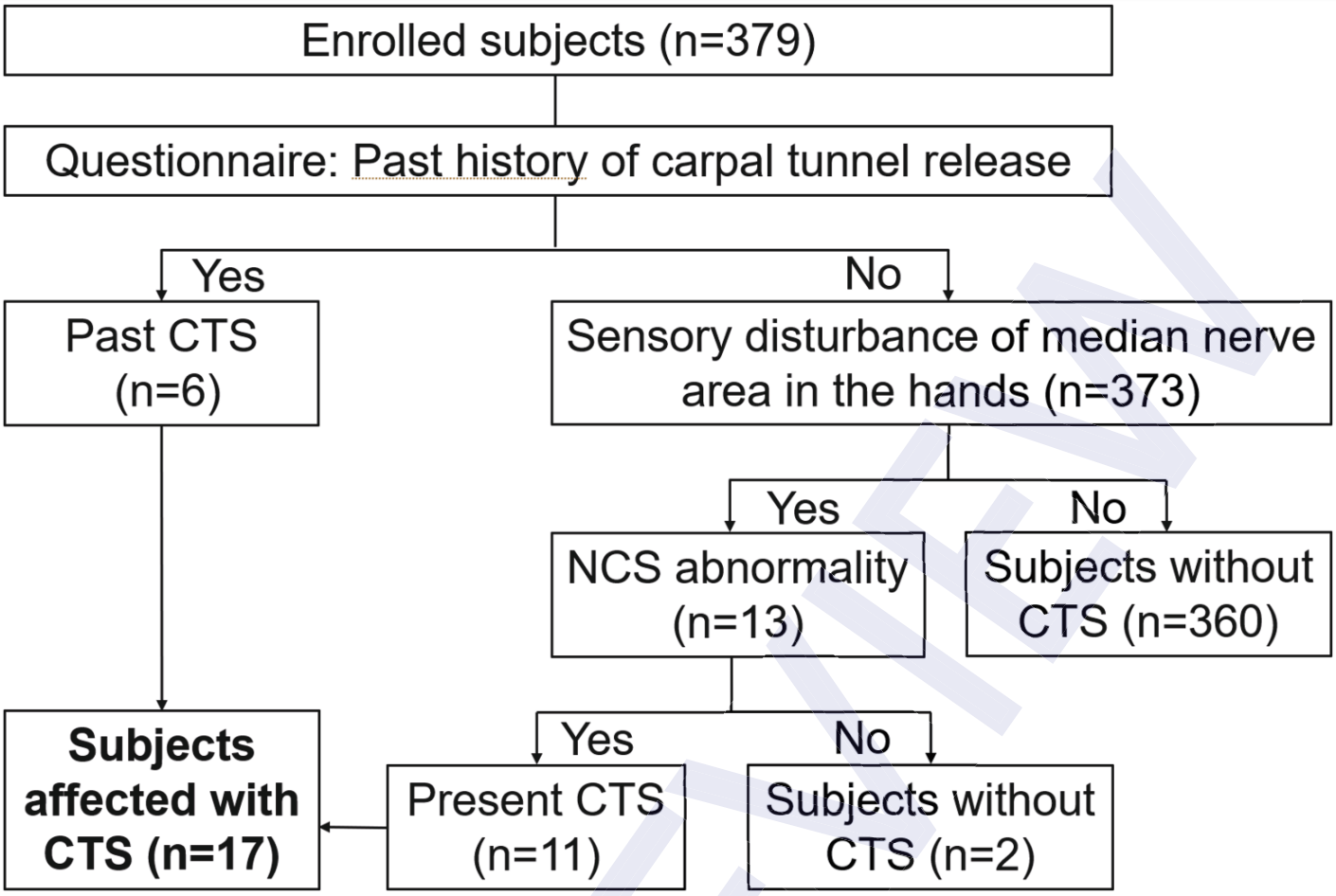


Fig. 5. Flowchart of carpal tunnel syndrome (CTS) diagnosis. Subjects with either past or present CTS were defined as being affected with CTS.

正誤表

下記の通り、誤記がありましたので訂正いたします。

正誤箇所	誤	正
本文 165 行目	“Of the 4 prospective randomized population-based studies identified in a PubMed search (Table 5), only 2 considered both clinical symptoms **and NCSs.[7,8] in CTS** diagnosis.”	“Of the 4 prospective randomized population-based studies identified in a PubMed search (Table 5), only 2 considered both clinical symptoms **and NCSs[7,8] in CTS** diagnosis.”
Table 4	引用文献の症例数に修正あり、修正後の Table 4 を別刷りした。修正箇所を下線で示した。	

Table 4

Prevalence of CTS in previous prospective studies

Author	Country	Subject population	Diagnostic criteria	No. of subjects Total (Female/Male)	Age of subjects (years)	Prevalence of CTS Total (Female/Male)
De Krom MC, et al.[7)]	Netherlands	Local government registry	Questionnaire and NCSs	504 (340/164)	25-74	(6.8%/0.6%)
Atroshi I, et al.[8)]	Sweden	Local government registry	Clinical examination and NCSs	2466 (1332/1134)	25-74	2.7% (3.0%/2.1%)
Tanaka S, et al.[9)]	United States	National health interview survey	Questionnaire	44233	18 or older	1.6% (1.9%/1.2%)
Shiri R, et al.[11)]	Finland	National health examination survey	Clinical examination	6254 (3410/2844)	30 or older	(5.3%/2.1%)
Present Study	Japan	Local government registry	Questionnaire and NCSs	379 (190/189)	50-89	4.7% (7.2%/1.8%)*

CTS: carpal tunnel syndrome, NCSs: nerve conduction studies.

* Weighted prevalence adjusted by Japanese national gender and age population values for ages 50–89 years.