guidelines (8). Therefore, identified pathogens that were not susceptible to β-lactams (ceftriaxone or ampicillin-sulbactam), macrolides (azithromycin or clarithromycin), and fluoroquinolones (moxifloxacin, levofloxacin, or garenoxacin) were defined as CAP-DRPs.

Statistical Analysis

Statistical analyses were performed using PASW Statistics 18 (SPSS Inc., Chicago, IL). All tests were two-tailed and a P value less than 0.05 was considered statistically significant. Demographic, clinical, and microbiologic characteristics, and antibiotic use, were described. Here categorical data were summarized as frequencies in percentage and continuous data as median with interquartile range. Pearson chi-square test or Mantel extension test for trend was used for analyzing discrete variables, and the Wilcoxon rank sum test for continuous variables.

Variables were further examined for association with CAP drug resistance by univariable and multivariable logistic regression analysis. Odds ratios (ORs) and their 95% confidence intervals (CIs) were calculated. For the analysis of risk factors for CAP drug resistance, candidate factors were determined *a priori* referring to those published in previous reports (7, 8, 12, 29–31). At least five patients with CAP-DRPs per risk factor were needed for it to be included in the analysis (32). Based on the logistic regression findings of these risk factors, a predictive index was created by assigning risk scores based on the regression coefficients of the significant variables (33). Traditional 2 × 2 tables were used to calculate sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the predictive rule, the HCAP definition, and two previous prediction models (21, 22). The validity of the prediction rule was evaluated using the receiver operating characteristic (ROC) curve, compared with two previous prediction models (21, 22). Calculation procedures of these previous prediction rules are provided in the online supplement.

Subanalyses were performed after CAP-DRPs were classified into the following two groups: MRSA and CAP-DRPs other than MRSA (e.g., *P. aeruginosa* and extended-spectrum β-lactamase-producing Enterobacteriaceae). The risk factors for them were evaluated separately.

RESULTS

Participants and Baseline Characteristics

A total of 1,742 patients with pneumonia were assessed for eligibility, and 1,413 of whom (887 with CAP and 526 with HCAP) were included in the study (Figure 1). The baseline characteristics of patients with CAP and HCAP are described in Table 1. Advanced age, neoplastic diseases, congestive heart failure, central nervous system disorders, and severe pneumonia were more frequent in patients with HCAP than in those with CAP. Frequency of hypoalbuminemia, previous use of antibiotics, use of gastric acid suppressive–agents, tube feeding, nonambulatory status, and positive MRSA history was higher in patients with HCAP than in those with CAP.

Identified Pathogens

Pathogens were identified in 475 (53.6%) of 887 patients with CAP and 320 (60.8%) of 526 patients with HCAP. Pathogen distribution according to type of pneumonia is shown in Table 2, and additional descriptions are shown in the online supplement. In patients with CAP, *S. pneumoniae* (17.1%) and *Haemophilus influenzae* (10.4%) were the two most frequently isolated pathogens. In patients with HCAP, *Klebsiella pneumoniae* (15.6%) was isolated most frequently, followed by *S. pneumoniae* (12.7%), MRSA (10.8%), methicillin-susceptible *S. aureus* (9.9%), and *P. aeruginosa* (8.7%).

Initial Antibiotics

Initially prescribed antibiotics are shown in Table 3. Patients with HCAP received monotherapy more frequently than patients with CAP. Antipseudomonal antibiotics were given to 22.4% of patients with CAP and 31.2% of patients with HCAP as initial empirical therapy. However, only 0.2 and 1.3% of patients with CAP and HCAP, respectively, received anti-MRSA antibiotics, although MRSA was detected in 2.3 and 10.8% of patients with CAP and HCAP, respectively.

Drug-Resistant Pathogens, IIAT, and Mortality

Microbiologic and clinical outcomes are shown in Table 4. Among patients with identified pathogens, CAP-DRPs were more frequently isolated in patients with HCAP (26.6%) than in those with CAP (8.6%). Regarding the relationship between IIAT and the occurrence of CAP-DRPs, IIAT was administered in 71.1% (27 of 38) and 10.2% (41 of 403) of patients with CAP with and without CAP-DRPs, respectively. In patients with HCAP with and without CAP-DRPs, IIAT was administered in 85.0% (68 of 80) and 13.0% (29 of 223), respectively. The proportion of patients receiving mechanical ventilation was similar between patients with CAP and HCAP. Thirty-day mortality was higher in patients with HCAP (20.3%) than in those with CAP (7.0%), and in-hospital mortality was also higher in HCAP (24.9%) than in CAP (10.0%). In patients with and without CAP-DRPs, the 30-day mortality was 21.0% (25 of 119) and 10.2% (64 of 627), respectively.

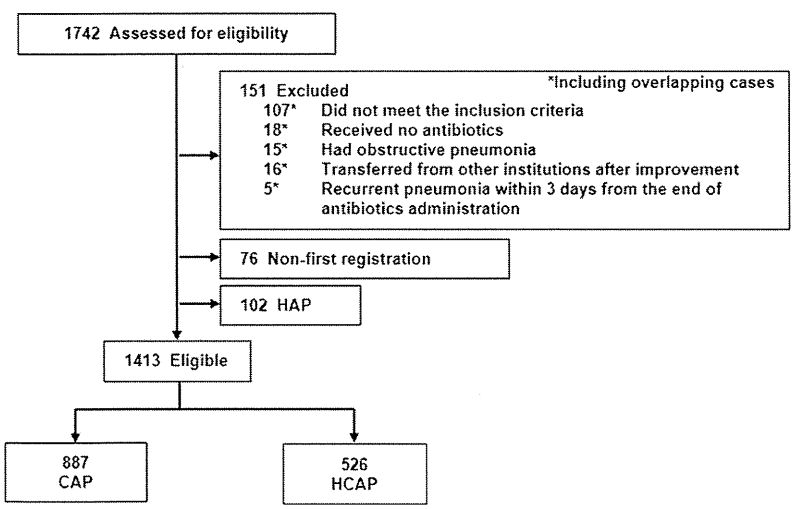


Figure 1. Patient flow. CAP = community-acquired pneumonia; HAP = hospital-acquired pneumonia; HCAP = healthcare-associated pneumonia.

TABLE 1. BASELINE CHARACTERISTICS OF THE STUDY PATIENTS

Variables	CAP ($n = 887$)	HCAP ($n = 526$)	P Value
Male, n (%)	580 (65.4)	335 (63.7)	0.518
Age, yr, median (IQR)	75 (66–83)	79 (70–85)	<0.001
Hospitalization for 2 days or more during the preceding 90 d, n (%)	—	246 (46.8)	—
Residence in a nursing home or extended care facility, n (%)	—	224 (42.6)	—
Home intravenous therapy (including antibiotics and chemotherapy), n (%)	—	137 (26.0)	—
Chronic dialysis during the preceding 30 d, n (%)	—	21 (4.0)	—
Home wound care during the preceding 30 d, n (%)	—	35 (6.7)	—
Comorbidities, n (%)			
Neoplastic diseases	111 (12.5)	97 (18.4)	0.002
Chronic lung diseases	309 (34.8)	161 (30.6)	0.103
Congestive heart failure	98 (11.0)	85 (16.2)	0.006
Chronic renal diseases	64 (7.2)	49 (9.3)	0.159
Chronic liver diseases	35 (3.9)	18 (3.4)	0.616
CNS disorders	139 (15.7)	165 (31.4)	<0.001
Diabetes	160 (18.0)	98 (18.6)	0.780
Immunosuppression*	58 (6.5)	40 (7.6)	0.446
Physical findings, n (%)			
Orientation disturbance (confusion)	121 (13.6)	153 (29.1)	<0.001
Systolic blood pressure < 90 mm Hg	37 (4.2)	44 (8.4)	0.001
Pulse rate ⩾ 125/min	73 (8.2)	67 (12.7)	0.006
Respiration rate ⩾ 30/min†	182 (21.1)	132 (25.6)	0.054
Laboratory findings			
BUN, mg/dl, median (IQR)	19.0 (13.3–27.0)	21.3 (14.5–31.2)	<0.001
Pao_2/FIo_2,‡ median (IQR)	291 (231–347)	256 (181–319)	<0.001
Hematocrit, %, median (IQR)	36.7 (33.1–40.1)	34.9 (31.0–38.3)	<0.001
C-reactive protein, mg/dl, median (IQR)	12.0 (6.2–19.1)	10.5 (4.8–16.2)	0.001
Albumin < 3.0 mg/dl, n (%)	225 (25.5)	253 (48.3)	<0.001
Radiographic findings, n (%)			
Bilateral lung involvement	374 (42.2)	275 (52.3)	<0.001
Use of antibiotics within the previous 90 d, n (%)	246 (27.7)	292 (55.5)	<0.001
Use of gastric acid suppressive agents (H_2-blockers or proton pump inhibitors), n (%)	199 (22.4)	169 (32.1)	<0.001
Tube feeding, n (%)	7 (0.8)	54 (10.3)	<0.001
Nonambulatory status,§ n (%)	89 (10.0)	249 (47.3)	<0.001
Positive MRSA history within the previous 90 d, n (%)	1 (0.1)	22 (4.2)	<0.001
PSI class,‖ n (%)			<0.001¶
I–III	358 (42.4)	83 (16.5)	
IV	320 (37.9)	214 (42.6)	
V	167 (19.8)	205 (40.8)	

Definition of abbreviations: BUN = blood urea nitrogen; CAP = community-acquired pneumonia; CNS = central nervous system; H_2-blockers = histamine H_2-receptor blocker; HCAP = healthcare-associated pneumonia; IQR = interquartile range; MRSA = methicillin-resistant *Staphylococcus aureus*; PSI = Pneumonia Severity Index.

* Immunosuppression included any immunosuppressive diseases, such as congenital or acquired immunodeficiency, hematologic diseases, and neutropenia (<1,000/mm^3), treatment with immunosuppressive drugs within the previous 30 days, or corticosteroids in daily doses of at least 10 mg/day of a prednisone equivalent for more than 2 weeks.

† Respiration rate was evaluated in 863 patients with CAP and 516 patients with HCAP.

‡ Arterial blood gas analysis was performed in 866 patients with CAP and 508 patients with HCAP. In cases where arterial blood gas analyses were not performed, Pao_2 was estimated from Spo_2.

§ Nonambulatory status was defined as being bedridden or using a wheelchair because of difficulty walking.

‖ The PSI was evaluated in 845 patients with CAP and 502 patients with HCAP.

¶ Trend test.

Risk Factors for CAP Drug-Resistant Pathogens

In the provisional analysis (*see* Table E1 in the online supplement), the significant risk factors for CAP-DRPs in patients with CAP included previous use of antibiotics; use of gastric acid–suppressive agents (histamine H_2-receptor blockers or proton pump inhibitors); tube feeding; and nonambulatory status. Similarly, the significant risk factors for CAP-DRPs in patients with HCAP were previous use of antibiotics, use of gastric acid–suppressive agents, tube feeding, and nonambulatory status. Therefore, assessment of risk factors was performed combining data for patients with CAP and HCAP, and using the definitional components of HCAP (Table 5). The independent risk factors for CAP-DRPs were as follows: hospitalization for 2 days or more during the preceding 90 days (adjusted OR [AOR], 2.06; 95% CI, 1.23–3.43); immunosuppression (AOR, 2.31; 95% CI, 1.05–5.11); use of antibiotics within the previous 90 days (AOR, 2.45; 95% CI, 1.51–3.98); use of gastric acid–suppressive agents (AOR, 2.22; 95% CI, 1.39–3.57); tube feeding (AOR, 2.43; 95% CI, 1.18–5.00); and nonambulatory status (AOR, 2.45; 95% CI, 1.40–4.30). These results were almost unchanged when the severity of illness (Pneumonia Severity

TABLE 2. IDENTIFIED PATHOGENS ACCORDING TO TYPE OF PNEUMONIA*

Microbes	CAP ($n = 887$)	HCAP ($n = 526$)
Identified	475 (53.6)	320 (60.8)
Gram-positive pathogens		
Streptococcus pneumoniae	152 (17.1)	67 (12.7)
Methicillin-susceptible *Staphylococcus aureus*	68 (7.7)	52 (9.9)
Methicillin-resistant *S. aureus*	20 (2.3)	57 (10.8)
Streptococci other than *S. pneumoniae*	23 (2.6)	31 (5.9)
Enterococcus sp.	0	3 (0.6)
Gram-negative pathogens		
Haemophilus influenzae	92 (10.4)	26 (4.9)
Klebsiella pneumoniae	77 (8.7)	82 (15.6)
ESBL+	2 (0.2)	1 (0.2)
Pseudomonas aeruginosa	33 (3.7)	46 (8.7)
Moraxella catarrhalis	32 (3.6)	12 (2.3)
Escherichia coli	26 (2.9)	22 (4.2)
ESBL+	4 (0.5)	5 (1.0)
Enterobacter sp.	15 (1.7)	12 (2.3)
Klebsiella oxytoca	7 (0.8)	9 (1.7)
Serratia marcescens	4 (0.5)	5 (1.0)
Citrobacter sp.	4 (0.5)	1 (0.2)
Acinetobacter sp.	4 (0.5)	8 (1.5)
Stenotrophomonas maltophilia	4 (0.5)	2 (0.4)
Other Enterobacteriaceae	4 (0.5)	3 (0.6)
Other nonfermenting gram-negative bacteria	3 (0.3)	1 (0.2)
Proteus group	2 (0.2)	8 (1.5)
ESBL+	0	2 (0.4)
Other gram-negative pathogens	3 (0.3)	2 (0.4)
Atypical pathogens	48 (5.4)	26 (4.9)
Mycoplasma pneumoniae†	11 (1.2)	4 (0.8)
Chlamydophila pneumoniae‡	31 (3.5)	21 (4.0)
Legionella pneumoniae	7 (0.8)	2 (0.4)
Others	4 (0.5)	5 (1.0)
Unidentified	412 (46.4)	206 (39.2)

Definition of abbreviations: CAP = community-acquired pneumonia; ESBL = extended-spectrum β-lactamase-producing; HCAP = healthcare-associated pneumonia.

* Data are presented as n (%).

† Serologic tests for *Mycoplasma pneumoniae* were performed in 307 patients with CAP and 123 patients with HCAP, and positive test results were obtained in 11 and 4, respectively.

‡ Serologic tests for *Chlamydophila pneumoniae* were performed in 260 patients with CAP and 94 patients with HCAP, and positive test results were obtained in 31 and 21, respectively.

TABLE 3. INITIALLY PRESCRIBED ANTIBIOTICS ACCORDING TO TYPE OF PNEUMONIA*

Antibiotics	CAP (*n* = 887)	HCAP (*n* = 526)
Monotherapy	442 (49.8)	356 (67.7)
β-Lactams	427 (48.1)	352 (66.9)
Quinolones	10 (1.1)	3 (0.6)
Other	5 (0.6)	1 (0.2)
Combination therapy	445 (50.2)	170 (32.3)
β -Lactams + macrolides	312 (35.2)	81 (15.4)
β -Lactams + minocycline	11 (1.2)	5 (1.0)
β -Lactams + quinolones	71 (8.0)	38 (7.2)
β -Lactams + aminoglycosides	1 (0.1)	2 (0.4)
β -Lactams + clindamycin	27 (3.0)	28 (5.3)
β -Lactams + anti-MRSA antibiotics†	1 (0.1)	4 (0.8)
β -Lactams + quinolones + anti-MRSA antibiotics†	1 (0.1)	2 (0.4)
Other combinations	21 (2.4)	10 (1.9)
Antipseudomonal antibiotics used‡	199 (22.4)	164 (31.2)
Anti-MRSA antibiotics used†	3 (0.2)	7 (1.3)

Definition of abbreviations: CAP = community-acquired pneumonia; HCAP = healthcare-associated pneumonia; MRSA = methicillin-resistant *Staphylococcus aureus*.

* Data are presented as n (%).

† Vancomycin, linezolid, teicoplanin, and arbekacin were defined as anti-MRSA antibiotics.

‡ Piperacillin-tazobactam, piperacillin, ceftazidime, cefepime, cefozopran, cefoperazone-sulbactam, aztreonam, imipenem-cilastatin, meropenem, doripenem, biapenem, ciprofloxacin, pazufloxacin, tobramycin, isepamycin, amikacin, and arbekacin were defined as antipseudomonal antibiotics.

TABLE 4. OUTCOMES ACCORDING TO TYPE OF PNEUMONIA*

Microbiologic and clinical outcomes	CAP (*n* = 887)	HCAP (*n* = 526)	*P* Value
Multidrug-resistant pathogens	45/475 (9.5)	74/320 (23.1)	<0.001
CAP drug-resistant pathogens†, ‡	38/442 (8.6)	81/304 (26.6)	<0.001
Inappropriate initial antibiotic treatment‡, §	69/442 (15.6)	99/305 (32.5)	<0.001
Mechanical ventilation‖	87 (9.8)	44 (8.4)	0.366
30-d mortality¶	62 (7.0)	107 (20.3)	<0.001
In-hospital mortality	89 (10.0)	131 (24.9)	<0.001

Definition of abbreviations: CAP = community-acquired pneumonia; HCAP = healthcare-associated pneumonia.

* Data are presented as n (%).

† Identified pathogens that were not susceptible to β-lactams (ceftriaxone or ampicillin-sulbactam), macrolides (azithromycin or clarithromycin), and fluoroquinolones (moxifloxacin, levofloxacin, or garenoxacin) were defined as CAP drug-resistant pathogens. Major CAP drug-resistant pathogens in CAP included methicillin-resistant *Staphylococcus aureus* (47.6% [20 of 42]), *Pseudomonas aeruginosa* (23.8% [10 of 42]), and extended-spectrum β-lactamase-producing Enterobacteriaceae (11.9% [5 of 42]); and those in HCAP included methicillin-resistant *S. aureus* (61.3% [57 of 93]), *P. aeruginosa* (20.4% [19 of 93]), and extended-spectrum β-lactamase-producing Enterobacteriaceae (6.5% [6 of 93]).

‡ CAP drug resistance and appropriateness of initial antibiotics was assessed in patients with the results of susceptibility testing of identified pathogens.

§ Antibiotic treatment was classified as inappropriate when the identified pathogens were not susceptible to the initially prescribed antibiotics, on the basis of *in vitro* susceptibility testing.

‖ Noninvasive positive-pressure ventilation was included.

¶ Patients who were discharged or transferred to other hospitals within 30 days with improvement of pneumonia were considered alive.

Index class V or A-DROP scores ⩾ 3) was included as a factor (24, 25).

Prediction Rule for CAP Drug-Resistant Pathogens

ORs of individual risk factors were 2.0–2.5. Therefore, a prediction rule for the CAP-DRP occurrence was constructed using a simple counting of the number of risk factors (Figure 2). As shown in Figure 2A, no risk factors or only one risk factor was identified in 86.4% of patients with CAP, two risk factors were identified in 10.9% of these patients, and three or more risk factors were identified in 2.7% of these patients. However, no risk factors or only one risk factor was observed in 35.9% of patients with HCAP, two risk factors were counted in 30.9% of these patients, and three or more risk factors were identified in 33.2% of these patients. Compared with patients with CAP, therefore, multiple risk factors for CAP-DRPs were present in patients with HCAP. When data for patients with CAP and HCAP were combined, the probability of the CAP-DRP occurrence was 3.5, 9.2, 21.8, 42.7, 53.8, and 83.3% in patients with zero, one, two, three, four, and five to six risk factors, respectively (Figure 2B). The diagnostic performance of this simple counting of the number of risk factors and the HCAP definition were as follows: sensitivity of 73.1% and specificity of 73.2%, with values of PPV of 34.1% and NPV of 93.5% of two or more risk factors; sensitivity of 47.1% and specificity of 90.9%, with values of PPV of 49.6% and NPV of 90.0% of three or more risk factors; and sensitivity of 68.1% and specificity of 64.4%, with values of PPV of 26.6% and NPV of 91.4% of the HCAP definition, respectively (*see* Table E2). Figure 3 shows the ROC curves for our counting method of the number of risk factors and for the two previous prediction rules. The area under the ROC curve (AU-ROC) for our method was 0.79 (95% CI, 0.74–0.84), and it was greater than 0.71 (95% CI, 0.66–0.77) of Shorr's scoring, and 0.66 (95% CI, 0.61–0.71) of Aliberti's scoring. When a predictive index based on the log-transformed ORs of the six risk factors was calculated for individuals, the AU-ROC was 0.79 (95% CI, 0.74–0.84). Additional results regarding the relationship between the number of risk factors and disease severity is shown in the online supplement.

Subanalyses of Risk Factors for MRSA and CAP Drug-Resistant Pathogens Other than MRSA

Risk factors for MRSA and CAP-DRPs other than MRSA were separately evaluated among combined patients with CAP and HCAP. The details of the results are provided in the online supplement. Comparing the risk factors for all CAP-DRPs with those for MRSA, the risk factors for MRSA included chronic dialysis during the preceding 30 days, positive MRSA history within the previous 90 days, and congestive heart failure, in addition to hospitalization for 2 days or more during the preceding 90 days, use of antibiotics within the previous 90 days, and use of gastric acid–suppressive agents. Regarding the risk factors for CAP-DRPs other than MRSA, the following five factors that were included in the risks for all CAP-DRPs were significant: (*1*) immunosuppression, (*2*) use of antibiotics within the previous 90 days, (*3*) use of gastric acid–suppressive agents, (*4*) tube feeding, and (*5*) nonambulatory status.

When counting the number of risk factors for all CAP-DRPs, the probabilities of both MRSA and CAP-DRPs other than MRSA were similar to that of all CAP-DRPs. Specifically, the probabilities of these two groups were low (<5%) in patients with no or one risk factor, and were high (28.3%) in patients with three or more risk factors (Table 6). There was a difference in the probabilities in patients with two risk factors between those two groups, that is, 17.6% for MRSA and 6.3% for CAP-DRPs other than MRSA. The AU-ROC of counting the number of risk factors for all CAP-DRPs was 0.76 (95% CI, 0.70–0.81) and 0.82 (95% CI, 0.75–0.88) for MRSA and CAP-DRPs other than MRSA, respectively. The probability of MRSA was increased in patients with two or more risk factors for all CAP-DRPs when considering any one of specific risk factors for MRSA (Table 6).

TABLE 5. RISK FACTORS FOR CAP DRUG RESISTANCE* IN PATIENTS WITH CAP AND HCAP COMBINED

Variables	Resistance		Univariable Analysis OR (95% CI)	Multivariable Analysis OR (95% CI)
	Yes	No		
Hospitalization for ⩾2 d during the preceding 90 d				
No (n = 604)	67	537	1 (ref)	1 (ref)
Yes (n = 142)	52	90	4.63 (3.03–7.09)	2.06 (1.23–3.43)
Residence in a nursing home				
No (n = 599)	78	521	1 (ref)	1 (ref)
Yes (n = 147)	41	106	2.58 (1.68–3.98)	1.13 (0.63–2.02)
Home intravenous therapy (including antibiotics and chemotherapy)				
No (n = 679)	107	572	1 (ref)	1 (ref)
Yes (n = 67)	12	55	1.17 (0.60–2.25)	0.84 (0.40–1.80)
Chronic dialysis during the preceding 30 d				
No (n = 734)	116	618	1 (ref)	1 (ref)
Yes (n = 12)	3	9	1.78 (0.47–6.66)	2.23 (0.51–9.69)
Home wound care during the preceding 30 d				
No (n = 726)	112	614	1 (ref)	1 (ref)
Yes (n = 20)	7	13	2.95 (1.15–7.56)	1.44 (0.47–4.39)
Immunosuppression				
No (n = 699)	104	595	1 (ref)	1 (ref)
Yes (n = 47)	15	32	2.68 (1.40–5.13)	2.31 (1.05–5.11)
Use of antibiotics within the previous 90 d				
No (n = 481)	46	435	1 (ref)	1 (ref)
Yes (n = 265)	73	192	3.60 (2.40–5.40)	2.45 (1.51–3.98)
Chronic lung disease				
No (n = 511)	77	434	1 (ref)	1 (ref)
Yes (n = 235)	42	193	1.23 (0.81–1.85)	1.13 (0.68–1.89)
Congestive heart failure				
No (n = 656)	97	559	1 (ref)	1 (ref)
Yes (n = 90)	22	68	1.86 (1.10–3.16)	1.68 (0.92–3.08)
CNS disorder				
No (n = 554)	73	481	1 (ref)	1 (ref)
Yes (n = 192)	46	146	2.08 (1.37–3.14)	1.36 (0.80–2.29)
Albumin < 3.0 mg/dl				
No (n = 468)	53	415	1 (ref)	1 (ref)
Yes (n = 274)	65	209	2.44 (1.63–3.63)	1.30 (0.81–2.09)
Use of gastric acid suppressive agents (H_2-blocker or PPI)				
No (n = 543)	64	479	1 (ref)	1 (ref)
Yes (n = 203)	55	148	2.78 (1.86–4.17)	2.22 (1.39–3.57)
Tube feeding				
No (n = 695)	94	601	1 (ref)	1 (ref)
Yes (n = 51)	25	26	6.15 (3.41–11.10)	2.43 (1.18–5.00)
Nonambulatory status				
No (n = 518)	51	467	1 (ref)	1 (ref)
Yes (n = 228)	68	160	3.89 (2.60–5.84)	2.45 (1.40–4.30)
Positive MRSA history within the previous 90 d				
No (n = 727)	109	618	1 (ref)	1 (ref)
Yes (n = 19)	10	9	6.30 (2.50–15.86)	2.47 (0.86–7.09)

Definition of abbreviations: CAP = community-acquired pneumonia; CI = confidence interval; CNS = central nervous system; H_2-blocker = histamine H_2-receptor blocker; HCAP = healthcare-associated pneumonia; MRSA = methicillin-resistant *Staphylococcus aureus*; OR = odds ratio; PPI = proton pump inhibitor; ref = reference.

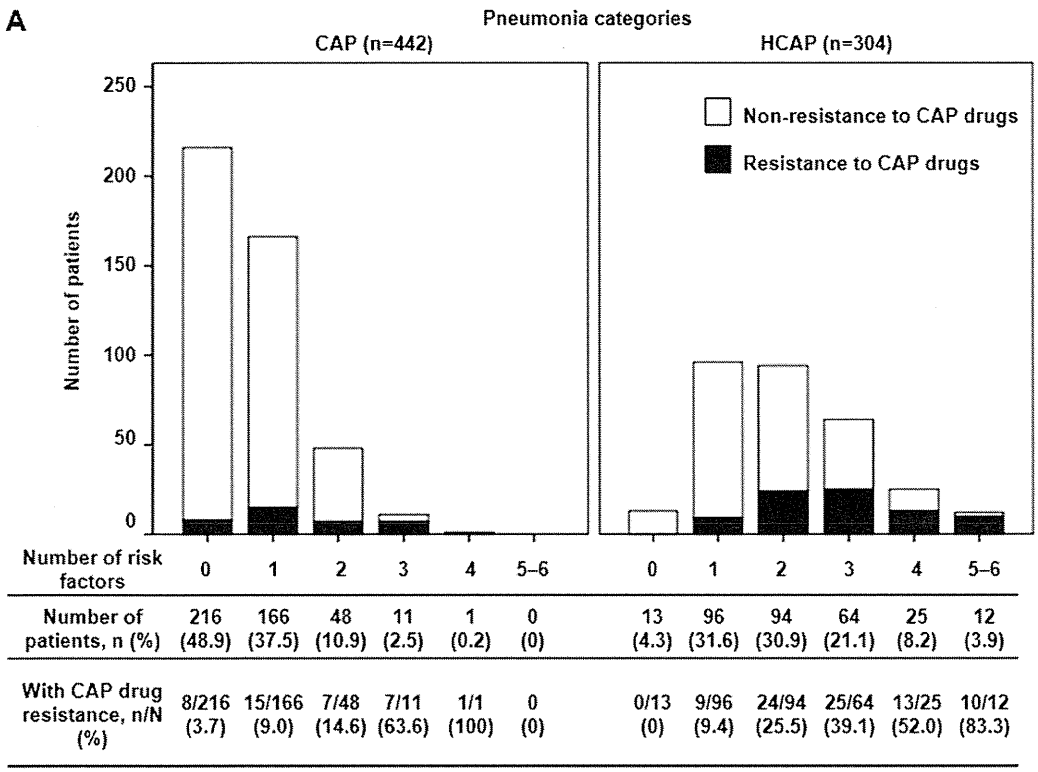
*Identified pathogens that were not susceptible to β-lactams (ceftriaxone or ampicillin-sulbactam), macrolides (azithromycin or clarithromycin), and fluoroquinolones (moxifloxacin, levofloxacin, or garenoxacin) were defined as CAP drug-resistant pathogens.

Administered Antibiotics and Clinical Outcome According to the Number of Risk Factors for CAP Drug-Resistant Pathogens

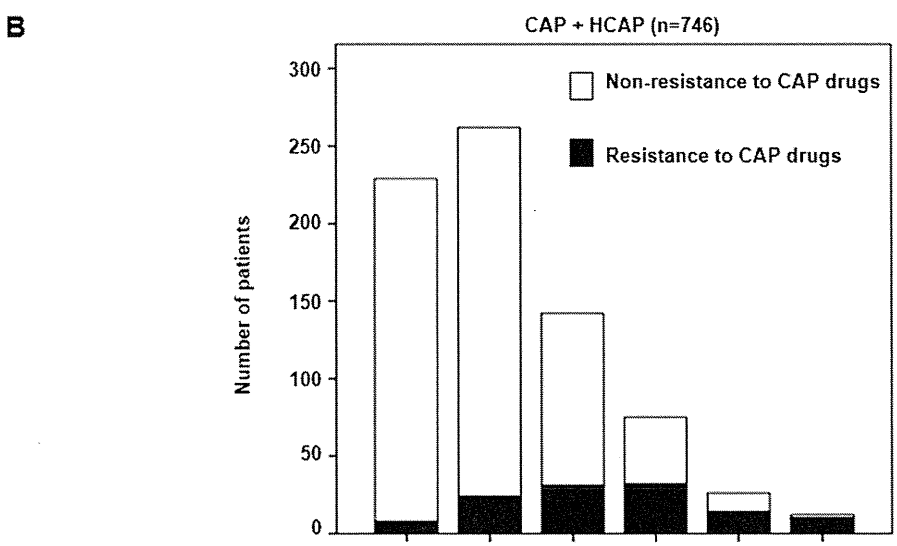
The relationships of the number of risk factors for CAP-DRPs to IIAT, administered antibiotics, and the 30-day mortality among patients who received their antibiotic treatment are shown in Table 6 and the additional descriptions are provided in the online supplement. Among patients with identified pathogens, IIAT was given in 14.7, 31.0, and 43.8% of patients with less than or equal to one, two, and three or more risk factors for CAP-DRPs, respectively. The 30-day mortality in patients who received IIAT in these three risk classes was 9.7% (7 of 72), 15.9% (7 of 44), and 28.6% (14 of 49), respectively. In these three risk classes, traditional antibiotic regimens of CAP drugs were administered in 155, 23, and 7 of patients with identified pathogens, respectively; and in 129, 24, and 6 of those without, respectively. The 30-day mortality in patients with less than or equal to one risk factor who received traditional regimens of CAP drugs was 1.3% (2 of 155) and 3.1% (4 of 129) in patients with and without identified pathogens, respectively. These 30-day mortality proportions were lower than those in patients who received monotherapy with nonantipseudomonal β-lactams, that is, 10.8% (22 of 203) in patients with identified pathogens and 9.6% (17 of 177) in those without, respectively.

DISCUSSION

In this multicenter, prospective, observational study, the clinical profile of HCAP was different from that of CAP concerning DRP identification. However, the risk factors for CAP drug resistance were almost identical in patients with CAP and HCAP.



Number of risk factors	0	1	2	3	4	5–6	0	1	2	3	4	5–6
Number of patients, n (%)	216 (48.9)	166 (37.5)	48 (10.9)	11 (2.5)	1 (0.2)	0 (0)	13 (4.3)	96 (31.6)	94 (30.9)	64 (21.1)	25 (8.2)	12 (3.9)
With CAP drug resistance, n/N (%)	8/216 (3.7)	15/166 (9.0)	7/48 (14.6)	7/11 (63.6)	1/1 (100)	0 (0)	0/13 (0)	9/96 (9.4)	24/94 (25.5)	25/64 (39.1)	13/25 (52.0)	10/12 (83.3)

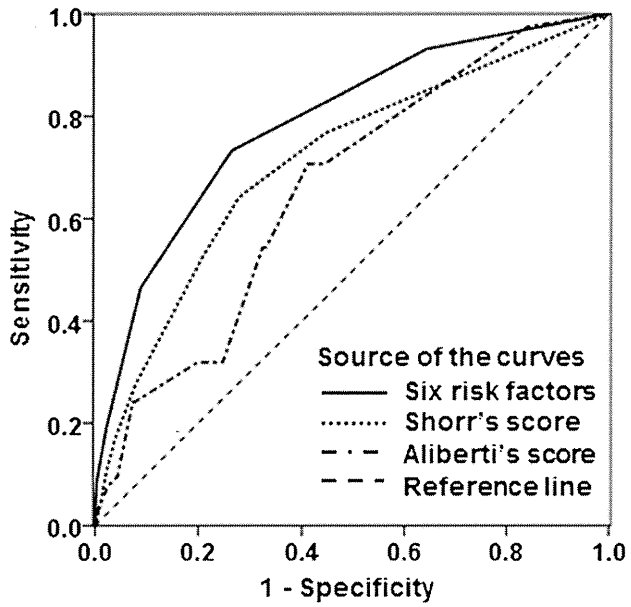


Number of risk factors	0	1	2	3	4	5–6
Number of patients, n (%)	229 (30.7)	262 (35.1)	142 (19.0)	75 (10.1)	26 (3.5)	12 (1.6)
With CAP drug resistance, n/N (%)	8/229 (3.5)	24/262 (9.2)	31/142 (21.8)	32/75 (42.7)	14/26 (53.8)	10/12 (83.3)

Figure 2. Number of risk factors for CAP drug resistance. Patients without identified pathogens were not included. CAP = community-acquired pneumonia; HCAP = healthcare-associated pneumonia.

As a result of this finding, a simple estimation of drug resistance was proposed using the counting of the number of risk factors (prior hospitalization, immunosuppression, previous use of antibiotics, use of gastric acid–suppressive agents, tube feeding, and nonambulatory status) irrespective of pneumonia category. An example of how this estimation system may be used is as follows. When no risk factors or only one risk factor is observed in a pneumonia patient, CAP-DRPs are lower (<10% in this study). For these patients (86% of patients with CAP and 36% of patients with HCAP in the current study), administration of broad-spectrum antibiotics should be curtailed, and CAP drugs should be given instead. When three or more risk factors are present, physicians should consider prescribing broad-spectrum antibiotics.

In this study, 30-day mortality and in-hospital mortality were higher in patients with HCAP than in those with CAP, as previously reported (10, 12, 13). More serious underlying conditions and treatment with monotherapy were more frequently observed in patients with HCAP than in those with CAP. The



Area under the curve

Test result variable(s)	Area	95% CI
Six risk factors	0.79	0.74–0.84
Shorr's score	0.71	0.66–0.77
Aliberti's score	0.66	0.61–0.71

Figure 3. The receiver operating characteristic (ROC) curves for prediction of community-acquired pneumonia drug resistance. CI = confidence interval. The six risk factors were as follows: prior hospitalization, immunosuppression, previous use of antibiotics, use of gastric acid–suppressive agents, tube feeding, and nonambulatory status. Shorr's score (range, 0–10) was calculated as the sum of the following weighted point assignments: 4, recent hospitalization; 3, nursing home; 2, chronic hemodialysis; and 1, critically ill (Pneumonia Severity Index class V). Aliberti's score (range, 0–12.5) was calculated as the sum of the following weighted point assignments: 5, chronic renal failure; 4, hospitalization for greater than or equal to 2 days or more in the preceding 90 days; 3, residence in a nursing home; and 0.5, one or more of cerebrovascular disease, diabetes, chronic lung disease (substitute for chronic obstructive pulmonary disease), antimicrobial therapy in preceding 90 days, immunosuppression, home wound care, and home infusion therapy.

frequency of receiving mechanical ventilation in patients with HCAP was similar to that in those with CAP, despite the fact that patients with HCAP had more severe disease than patients with CAP. These results suggest that differences in mortality between patients with these two types of pneumonia may be attributable to differences in personal characteristics and background and the resulting treatment restrictions, as suggested by Ewig and colleagues (3).

The spectrum of pathogens identified in patients with HCAP was different from that in patients with CAP. The pathogens in HCAP included those frequently found in both CAP and HAP (i.e., *S. pneumoniae*, *K. pneumoniae*, methicillin-susceptible *S. aureus*, MRSA, and *P. aeruginosa*) (9–12, 15, 34, 35). This finding was consistent with that of some previous studies (9, 11), but not with those of other studies (15, 16). The spectrum of pathogens may vary because of the wide range of clinical situations in which HCAP develops.

Although CAP-DRPs were more frequently found in patients with HCAP, the proportion was 26.6% at most. Thus, broad-spectrum antibiotic administration is not appropriate for treatment of all patients with HCAP, as suggested by Brito and Niederman (2). However, CAP-DRPs were found in 8.6% of patients with CAP. Thus, the type of pneumonia (CAP or HCAP) may not determine the presence or absence of CAP-DRPs. Other clinical factors may be at work. In this study, 22.4% of patients with CAP received antipseudomonal antibiotics, which may indicate an overuse of broad-spectrum antibiotics for patients with CAP. Furthermore, the discrepancy between the proportion of MRSA identification and that of initial administration of anti-MRSA antibiotics may suggest undertreatment for patients with MRSA. Because CAP-DRPs were strongly associated with IIAT in this study, identification of the risk factors associated with CAP-DRPs is crucial to ensure appropriate initial antibiotic treatment.

Here, six independent risk factors for CAP-DRPs were revealed in patients with CAP and HCAP. Because these risk factors were identical in CAP and HCAP, a prediction rule was developed combining the data for patients with these two types of pneumonia. Among the variables included in the HCAP definition, only hospitalization for 2 days or more during the preceding 90 days was statistically significant. Previous studies have proved the HCAP definition to be less accurate in predicting the occurrence of DRPs in patients with pneumonia (18, 19, 22). This study elucidated the importance of five other factors not included in the HCAP definition (i.e., use of antibiotics within the previous 90 d, immunosuppression, use of gastric acid–suppressive agents, tube feeding, and nonambulatory status). Although there was variation of the risk factors for drug resistance among studies, differences between our results and findings of previous studies may be attributable to the fact that some of the previously mentioned five factors were not available in previous studies (21, 36–39). Use of gastric acid–suppressive agents, which is known as a risk factor for the occurrence of CAP and HAP (40, 41), was newly identified to be a risk factor for drug resistance. Although increased pH levels in gastric juice have been associated with proliferation of bacteria (42), the connection between drug resistance acquisition and use of gastric acid–suppressive agents is a topic for future investigation.

This study indicated a difference in CAP drug resistance between patients with CAP and those with HCAP. This difference can be easily quantified by the cumulative risk factors for CAP-DRPs. These factors are common to both patients with CAP and HCAP. Therefore, a unified strategy of initial antibiotic selection for treatment of CAP and HCAP may be used.

Prediction of the presence or absence of DRPs at diagnosis is crucial in the treatment of pneumonia (20, 43). Recently, two research groups have developed scoring systems to predict drug resistance; these systems assign various weights to the respective risk factors (21, 22). However, a simpler method is preferable because of the high prevalence of this disease and the need for rapid decision-making about the most appropriate antibiotic regimen. Fortunately, the ORs of all independent risk factors included in this study were similar (2.0–2.5). Therefore, the proposed prediction rule for CAP drug resistance, which consisted of counting the number of risk factors observed in a given pneumonia patient, is feasible. In comparing the simple counting of the number of risk factors with the scoring system using their different weight based on the logistic regression findings in this study, the AU-ROC of these two methods were similar. Furthermore, the AU-ROC using this proposed method (0.79) was not inferior to 0.71 of Shorr's scoring and 0.79 of Aliberti's scoring that were published in their original reports (21, 22).

TABLE 6. ADMINISTERED ANTIBIOTICS AND CLINICAL OUTCOME IN EACH RISK GROUP OF CAP DRUG-RESISTANT PATHOGENS*

	Number of Risk Factors for CAP-DRPs†		
	≤1	2	≥3
Patients with identified pathogens‡, n	491	142	113
Drug-resistant pathogens			
All CAP-DRPs	32/491 (6.5)	31/142 (21.8)	56/113 (49.6)
CAP-DRPs other than MRSA	12/491 (2.4)	9/142 (6.3)	32/113 (28.3)
MRSA	20/491 (4.1)	25/142 (17.6)	32/113 (28.3)
MRSA in patients who had any one of specific risk factors for MRSA§	5/56 (8.9)	12/33 (36.4)	12/28 (42.9)
Inappropriate initial antibiotic treatment	72/490 (14.7)	44/142 (31.0)	49/112 (43.8)
Administered initial antibiotics			
Traditional regimens of CAP drugs‖	155/491 (31.6)	23/142 (16.2)	7/113 (6.2)
Monotherapy with nonantipseudomonal β-lactams¶	203/491 (41.3)	67/142 (47.2)	50/113 (44.2)
Antipseudomonal antibiotics	114/491 (23.2)	39/142 (27.5)	48/113 (42.5)
Anti-MRSA antibiotics	3/491 (0.6)	1/142 (0.7)	3/113 (2.7)
30-d mortality			
Overall	42/491 (8.6)	21/142 (14.8)	26/113 (23.0)
Inappropriate initial antibiotic treatment	7/72 (9.7)	7/44 (15.9)	14/49 (28.6)
Traditional regimens of CAP drugs**	2/155 (1.3)	3/23 (13.0)	0/7 (0)
Monotherapy with nonantipseudomonal β-lactams††	22/203 (10.8)	11/67 (16.4)	11/50 (22.0)
Patients without identified pathogens, n	439	122	57
Administered initial antibiotics			
Traditional regimens of CAP drugs‖	129/439 (29.4)	24/122 (19.7)	6/57 (10.5)
Monotherapy with nonantipseudomonal β-lactams¶	177/439 (40.3)	52/122 (42.6)	28/57 (49.1)
Antipseudomonal antibiotics	93/439 (21.2)	40/122 (32.8)	20/57 (35.1)
Anti-MRSA antibiotics	0/439 (0)	2/122 (1.6)	1/57 (1.8)
30-d mortality			
Overall	38/439 (8.7)	22/122 (18.0)	13/57 (22.8)
Traditional regimens of CAP drugs**	4/129 (3.1)	1/24 (4.2)	1/6 (16.7)
Monotherapy with nonantipseudomonal β-lactams††	17/177 (9.6)	14/52 (26.9)	7/28 (25.0)

Definition of abbreviations: CAP = community-acquired pneumonia; CAP-DRP = CAP drug-resistant pathogen; MRSA = methicillin-resistant *Staphylococcus aureus*.

* Data are presented as n (%) unless indicated otherwise.

† Risk factors for CAP-DRPs include prior hospitalization, immunosuppression, previous use of antibiotics, use of gastric acid–suppressive agents, tube feeding, and nonambulatory status.

‡ Patients in whom susceptibilities of pathogens to CAP drugs could not be assessed were not included.

§ Specific risk factors for MRSA include chronic dialysis, positive MRSA history, and congestive heart failure.

‖ Traditional regimens of CAP drugs include the following regimens: combination therapy with β-lactams (ceftriaxone or ampicillin-sulbactam) plus macrolides (azithromycin, clarithromycin, or erythromycin) or monotherapy with fluoroquinolones (moxifloxacin, levofloxacin, or garenoxacin).

¶ Nonantipseudomonal β-lactams include the following antibiotics: ampicillin, ampicillin-sulbactam, ceftriaxone, and cefotaxime.

** β-Lactams (ceftriaxone or ampicillin-sulbactam) plus macrolides (azithromycin, clarithromycin, or erythromycin) were administered to all of 185 patients with identified pathogens. In 159 patients without identified pathogens, β-lactams plus macrolides and monotherapy with a fluoroquinolone (levofloxacin) were administered to 156 and 3 of them, respectively.

†† Ampicillin-sulbactam, ceftriaxone, and cefotaxime were administered to 178, 141, and 1 patient with identified pathogens, respectively. Ceftriaxone, ampicillin-sulbactam, and ampicillin were administered to 136, 120, and 1 patient without identified pathogens, respectively.

Therefore, the proposed simple prediction rule is a useful addition in clinical settings. Validation studies are awaited.

In 86% of patients with CAP and 36% of patients with HCAP in this study, no risk factors or only one risk factor were identified. Administration of CAP drugs to these patients would be acceptable because the risk of resistance to these drugs was low (<10%). Therefore, administration of broad-spectrum antibiotics should be refrained for patients of this low-risk group. In fact, 30-day mortality was low (≤3.1%) in patients who received traditional regimens of CAP drugs including combination therapy with β-lactams plus macrolides. Regarding administration of CAP drugs, monotherapy with nonantipseudomonal β-lactams may not be suitable as reported previously (44–46). However, for patients with CAP and HCAP with three or more risk factors, the risk of resistance to CAP drugs was high (>40%). Broad-spectrum antibiotics should be considered for these patients. Physicians should take into account the fact that the frequency of IIAT and the 30-day mortality in patients who received IIAT increased as the risks for CAP-DRPs rose in this study. Patients with two risk factors were at intermediate risk (~20%). In this group, the probabilities of MRSA and CAP-DRPs other than MRSA were 17.6% and 6.3%, respectively. Therefore, in patients with two or more risk factors, administration of anti-MRSA antibiotics should be considered for patients with the specific risk factors for MRSA (i.e., chronic dialysis, positive MRSA history, and congestive heart failure). Administration of antipseudomonal antibiotics should be curtailed in patients with two or less risk factors, and should be limited to those with three or more risk factors. The effectiveness of initial antibiotics in each risk group should be validated in future interventional studies.

This study has some limitations. First, patients enrolled in this study were all hospitalized. Therefore, the results of this study should not be applied in a straightforward manner to outpatients. Second, the pathogens identified in this study may not have been the cause of pneumonia. Laboratory samples were obtained from only sputa in as many as about 80% of patients with CAP and HCAP. Furthermore, the cultures were performed semiquantitatively rather than quantitatively. However, avoiding invasive procedures to obtain samples from lower respiratory tracts and semiquantitative culturing are common in clinical settings; thus, the results obtained in this study would be clinically relevant. A methodology for determining causative pathogens semiquantitatively and using sputa must be developed in future studies. Third, the period of patient enrollment did not include

the influenza season because a sufficient number of patients with pneumonia were registered by 2010 early winter. Finally, to deal with potential colinearity of the risk factors for CAP-DRPs, alternative statistical analysis, such as a regression tree method, might give better discrimination and be worthy of exploration. Despite these limitations, we believe that the associations between patient profile and drug resistance identified in this study are robust.

In conclusion, this multicenter, prospective, observational study examined the clinical and microbiologic features of hospitalized patients with CAP and HCAP. Risk factors for CAP-DRPs were identical in patients with CAP and HCAP. A new prediction rule for drug resistance was proposed that is applicable to patients in these two groups. This simple and feasible prediction rule involves the simple counting of the number of risk factors to determine appropriate initial antibiotic treatment for patients with pneumonia.

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Factors Associated With Weight Gain After Smoking Cessation Therapy in Japan

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▶ ***Background:*** Smoking cessation is often followed by weight gain, which may attenuate motivation to sustain a quit attempt.

▶ ***Objectives:*** The aim was to identify factors associated with weight gain in smokers who received smoking cessation therapy (SCT) in Japan.

▶ ***Methods:*** The weight change in 283 smokers between baseline and 12 months after finishing SCT was observed. Factors associated with marked weight gain of 3.5 kg or more were identified using stepwise logistic regression.

▶ ***Results:*** Smoking cessation success was 83% (234/283) at the completion of SCT but decreased to 69% (194/283) 12 months later. Twelve months after the end of SCT, age 50 and over (*OR* = 0.38, 95% CI [0.19, 0.76]) and varenicline use (*OR* = 0.30, 95% CI [0.11, 0.78]) were protected against marked weight gain, whereas presence of a comorbidity (*OR* = 3.33, 95% CI [1.10, 10.00]), high level of nicotine dependence at baseline (*OR* = 2.07, 95% CI [1.09, 3.92]), and successfully quitting smoking (*OR* = 4.57, 95% CI [1.94, 10.08]) were associated with marked weight gain.

▶ ***Discussion:*** Understanding the factors associated with weight gain after smoking cessation can help in the design of nursing interventions to lessen or prevent weight gain among smokers who try to quit.

▶ ***Key Words:*** Japanese · risk factors · smoking cessation · weight gain

It is well known that smoking cessation is associated with weight gain (Aubin, Farley, Lycett, Lahmek, & Aveyard, 2012; Audrain-McGovern & Benowitz, 2011; Filozof, Fernandez Pinilla, & Fernandez-Cruz, 2004). Postcessation weight gain possibly attenuates motivation to engage or sustain a quit attempt that induces poorer cessation outcomes (Alberg, Carter, & Carpenter, 2007; Guirguis et al., 2010; Klesges et al., 1988). In addition, extreme smoking cessation-related weight gain partly contributes to increased risk of Type 2 diabetes (Davey Smith et al., 2005) and hypertension (Gerace, Hollis, Ockene, & Svendsen, 1991) compared to those who failed to stop smoking. Therefore, prevention of postcessation weight gain is important not only to help patients quit smoking but to prevent illnesses related to postcessation weight gain.

Factors Associated With Weight Gain

Factors associated with marked increase in body weight among patients who underwent smoking cessation were being African American, large number of cigarettes smoked per day, younger age, and low physical activity (Williamson et al., 1991). Other studies conducted in Western countries indicated that younger age, large number of cigarettes smoked per day, women, being overweight or obese at baseline, and success in quitting smoking were risk factors of weight gain through attempt of changing smoking behaviors (Klesges et al., 1997; Levine, Bush, Magnusson, Cheng, & Chen, 2013). A recent meta-analysis of 64 studies concerning weight gain at 12 months after smoking cessation found that the mean weight gain was 4.2 kg in varenicline users and 4.9 kg in no medication quitters (Aubin et al., 2012). Lycett, Munafo, Johnstone, Murphy, and Aveyard (2011) reported that there is an average weight gain of 8.8 kg after long-term smoking cessation of 8 years.

As most of these studies have been reported from Western countries, it is unclear whether the findings are applicable

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to the East Asian population who have a smaller body and lighter weight compared to the Western population. There are only a few previous studies on postcessation weight gain conducted in East Asian populations, including the Japanese population. One study reported that the average weight gain in varenicline users from China, Singapore, and Thailand was 1.7 kg (12 months after quitting; Wang et al., 2009). In a sample of Japanese smokers who quit, average weight gains were 3.5 and 4.6 kg at 18 and 30 months after cessation, respectively, after which subjects lost weight (Kadowaki et al., 2006). In a double-blind clinical trial of the efficacy and tolerability of varenicline (Nakamura et al., 2007), weight gain averaged 1.21–1.32 kg among those receiving doses of 0.25, 0.5, or 1.0 mg dose twice a day with weight gain slightly higher among successful quitters than among all treated; those in the no-treatment placebo group also gained weight (less when compared with all those who were treated and more in the comparison of successful quitters). From these results, it seems that Asian individuals who receive smoking cessation intervention show smaller weight gain than those from Western populations. However, there are some patients who have marked weight gain after smoking cessation therapy (SCT) in Japan.

Smoking in Japan

Smoking rates in Japanese adults have steadily declined to 32.4% among men and 9.7% among women in 2012 (Japan National Health and Nutrition Survey, 2012). A smoking ban policy has been in force in taxis, railway stations, parks, and many work places in the past 10 years.

There are two major smoking cessation programs in Japan. One program is provided by public health nurses at health checkups in occupational health clinics and health checkups of local residents, and the other program is SCT covered by the health insurance system. SCT has been covered by the Japanese medical insurance system starting from April 2006, and SCT was offered in approximately 14,000 hospitals and clinics in 2012. The SCT is standardized according to the Standard Procedures for Smoking Cessation Treatment, issued on March 2006 by the Japanese Circulation Society, Japan Lung Cancer Society, and Japanese Cancer Association (Shimada et al., 2011). Individuals who were motivated to stop smoking could receive the SCT covered by health insurance if they were assessed as having nicotine dependence defined by a Tobacco Dependence Screener score of ≥5 (Kawakami, Takatsuka, Inaba, & Shimizu, 1999) and a Brinkman index of ≥200 (Brinkman & Coates, 1963). The SCT consists of a total of five sessions: their first visit and 2, 4, 8, and 12 weeks thereafter. Patients are treated with either oral varenicline (standard use: 12 weeks) or nicotine patches (standard use: 8 weeks).

Varenicline is a selective $\alpha_4\beta_2$ nicotinic acetylcholine receptor partial agonist that relieves nicotine craving and withdrawal effects while reducing the reinforcing effects of nicotine through its partial agonist mechanism of action (Garrison & Dugan, 2009; Jamal, Dube, Malarcher, Shaw, & Engstrom, 2012). Varenicline is usually administered according to the following schedule: 0.5 mg per day on Days 1–3, 0.5 mg twice per day on Days 4–7, and then 1 mg twice per day through Week 12. As there is evidence that the success rate in varenicline users is higher than that in nicotine patch users (Wu, Wilson, Dimoulas, & Mills, 2006), Japanese physicians have suggested using varenicline as a first-line medication in the SCT programs. The most frequent side effect among Japanese varenicline users is gastrointestinal disorders including nausea, which affects about 25% of those prescribed varenicline (Tsukahara, Noda, & Saku, 2010).

At each SCT session, patients first meet briefly with a physician. Then, nurses trained in the SCT protocol meet with patients for about 10–30 minutes for specific advice concerning the continuation of cessation. Assessment of risk factors for postcessation weight gain is thought to be helpful in weight control intervention.

Purpose

There have been few studies to elucidate factors associated with increasing body weight after smoking cessation intervention in the East Asian population. Thus, this study observed the weight change in smokers who received Japanese SCT between the first visit to 12 months after the end of SCT. The aim of this study was to identify factors associated with marked weight gain after participating in SCT.

Theoretical Framework

The framework pictured in Figure 1 summarizes important factors related to smoking cessation and weight gain. Marked increase in body weight after smoking cessation intervention contributes to the risk of relapse (Alberg et al., 2007). Potential factors associated with postcessation weight gain are thought to be divided into three groups: (a) basic characteristics such as gender and age (Klesges et al., 1997; Saules, Pomerleau, Snedecor, Brouwer, & Rosenberg, 2004), (b) smoking-related factors such as the number of cigarettes smoked per day and intensity of craving (Saules et al., 2004; Williamson et al., 1991), and (c) whether the patient has success in quitting smoking or not (Eisenberg & Quinn, 2006). Little evidence about these factors is available based on research findings from East Asian populations. Elucidating risk factors for postcessation weight gain can provide important information for designing effective weight gain controls in smoking cessation interventions performed by nurses.

Methods

Setting, Participants, and Procedure

We conducted a multi-institutional study to monitor the effect of SCT and elucidate factors associated with success of smoking cessation in the SCT administered at six Japanese hospitals (Nagoya Medical Center, Aichi Cancer Center, Chukyo Hospital, Kinki-Chuo Chest Medical Center, Shikoku Cancer Center, and Kitazato Research Hospital). Study subjects were recruited among patients who received SCT for the first time between October 2008 and June 2011 and who provided written informed consent. This study was approved by the institutional review board of Aichi Cancer Center. Among 790 patients in the multi-institutional study, 447 participants who received at least four of the five sessions of SCT were enrolled in the follow-up survey. They were followed up at 3, 6, and 12 months after the end of SCT to obtain their body weight and smoking status. A mail-based self-report questionnaire

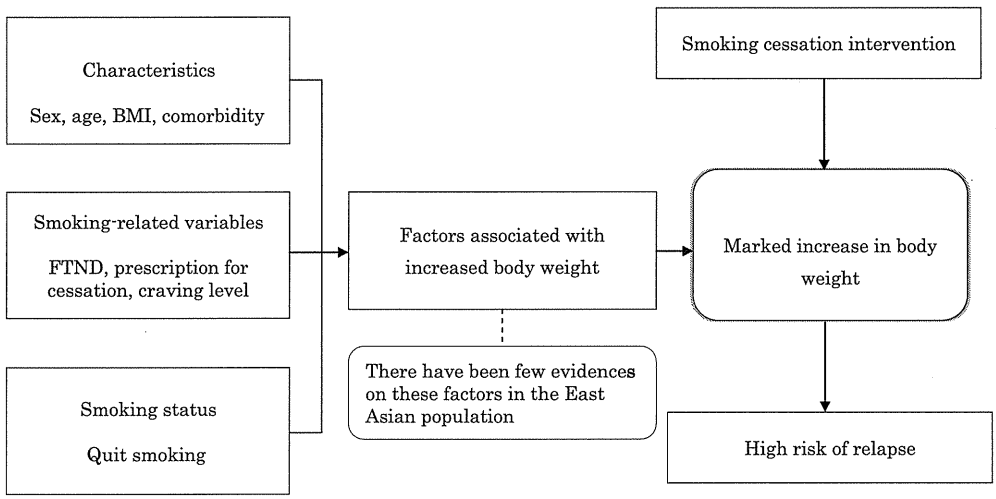

FIGURE 1. The theoretical framework of this study.

was used. For each of the three follow-up surveys, a reminder was sent to patients who had not returned the form within 2 weeks. Of these, 134 patients (30%) failed to return one or more follow-up surveys, and 30 (7%) participants sent an incomplete questionnaire. Data from the remaining 283 patients were used in the analysis.

Data Items

Demographic Data The study collected demographic information including age, gender, and presence of a comorbidity such as cardiovascular disease, cancer, or mental disorder with nicotine dependence. Smoking history was obtained using a self-report questionnaire at the first session.

Nicotine Dependence The Fagerström Test for Nicotine Dependence (FTND; Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991) was used to assess nicotine dependence. In this test, scores range from 0 to 10; scores of ≥7 indicated severe nicotine dependence. The FTND consists of six questionnaire items, including the number of cigarettes per day, time to the first cigarette of the day, nicotine yield, and so on. The FTND is a valid and reliable measurement tool (Pomerleau, Carton, Lutzke, Flessland, & Pomerleau, 1994), and it is commonly used in the setting of smoking cessation interventions.

Nicotine Craving The craving grade of patients was provided by their response to questions asked by physicians in every session on the following two axes: one is the strength of craving (0 = *I feel no craving for smoking anymore*, 1 = *I feel a need to put something in my mouth to cope with the craving*, 2 = *I need endurance to cope with the craving*, and 3 = *I can hardly continue to stop smoking because of a strong craving*) and the other is the number of times of craving that the patient feels per day (0 = *0 time per day*, 1 = *≤1 time per day*, 2 = *1–3 times per day*, 3 = *≥4 times per day*). This questionnaire was validated in patients who received SCT in Japan (Taniguchi & Tanaka, 2009). In this study, craving was defined as 0 = *negative* when both axes had a score of 0 at the last session and 1 = *positive* otherwise.

Prescription Information on prescription for smoking cessation (varenicline or nicotine patch) was collected from the medical record. Nausea was considered to be a side effect of the prescription if there were no other apparent causes.

Weight Change Body weight (in kilograms) was measured for each participant by nurses at every session. Participants were weighed with their clothes on but without shoes, jackets, or heavy outer garments. At the follow-up survey, participants measured their weight by themselves in the same manner. Weight change was calculated as the difference between the weight at the first session (before receiving SCT) and the weight at subsequent sessions or follow-ups.

Statistical Analysis

Transformations of Weight Data Covariates and outcomes were transformed to facilitate the analysis. Weight change was split into five categories: (a) less than −1.5 kg, (b) −1.5 to 1.5 kg, (c) 1.5 to 3.5 kg, (d) 3.5 to <5.5 kg, and (e) 5.5 kg and over. In the East Asian population, the mean body weight increase in patients who participated in smoking cessation was reported to be approximately 1–2 kg with standard deviation of 1.5–2.0 kg (Kadowaki et al., 2006; Mizoue, Ueda, Tokui, Hino, & Yoshimura, 1998; Nakamura et al., 2007). Therefore, a body weight increase of 3.5 kg (approximately mean + 1.0 *SD*) was defined as the cutoff for marked weight gain. It was computed between baseline and the end of SCT, and between baseline and 12 months after SCT.

Transformations of Covariates Covariates included gender, age (<50 years/≥50 years), presence of a comorbidity with nicotine dependence (absence/presence), body mass index (BMI) at the first session (<25/≥25), FTND score (<7/≥7), the number of cigarettes smoked per day (<30 per day/≥30 per day), prescription (varenicline/nicotine patch), nausea at the second session (2 weeks after the first session: absence/presence), craving at the last session (12 weeks after the first session: negative/positive), smoking status at the last session (quit/still smoking), and smoking status at 12 months after the end of SCT (quit/still smoking). Success in quitting smoking was defined at the last session when subjects replied that they quit smoking for at least the previous 2 weeks, which was verified by the CO concentration in exhaled breath (≤7 ppm). Participants

TABLE 1. Participant Demographics

Characteristic	*n*	%	*M*	*SD*
Sex (male)	200	70.7		
Age (years)			56.6	13.0
BMI (≥25)	89	31.5		
Comorbidity (present)	249	88.0		
Number of cigarettes per day			26.1	12.8
Brinkman index			890.0	540.9
FTND (≥7; nicotine dependent)	109	38.5		
Prescription (varenicline)[a]	249	88.0		
Craving at the second session (positive)	235	88.7		
Craving at the last session (positive)	58	23.9		

Note. $N = 283$. BMI = body mass index; FTND = Fagerström Test for Nicotine Dependence.
[a]The remaining subjects received a nicotine patch.

were considered to have successfully quit smoking if they reported at least 2 weeks of abstinence at 12 months after the end of SCT.

Statistical Tests The Mann–Whitney *U* test was used to identify the significance of differences between the subgroups defined by the five weight gain categories. Stepwise logistic regression was used to identify risk and protective factors associated with marked weight gain at the end of SCT and 12 months after the end of SCT, with the smoking status indicator from the same time period used as a covariate in each analysis. Nominal significance was set at $p < .05$. All statistical analyses were performed using STATA version 10 (STATA Corp., College Station, TX).

Results

Sample Description

Table 1 shows the characteristics of the 283 study subjects. Twenty-nine percent were women, 32% had a BMI of 25 and over, and 12% were free from a comorbidity with nicotine dependence. The mean age at the first session was 57 years. The mean BMI was 22.6 ($SD = 3.36$), which did not differ significantly from the average BMI of Japanese individuals in their 50s (male, 24.1; female, 22.5; Japan National Health and Nutrition Survey, 2009). Thirty-nine percent of the subjects (109 persons) showed high nicotine addiction as characterized by the FTND score of 7 and over. Varenicline was prescribed to 88% (249 persons), and nicotine patches were prescribed to the remaining 12% (34 persons). The proportion of subjects with a craving to smoke at the second and last sessions in the SCT was 89% and 24%, respectively.

Description of Weight Change

The mean body weight at baseline was 65.5 kg ($SD = 11.0$ kg) among men and 54.2 kg ($SD = 11.2$ kg) among women. The mean weight gain from baseline to the end of SCT was 1.4 kg ($SD = 2.6$ kg; $n = 200$) in men and 1.2 kg ($SD = 2.1$ kg; $n = 83$) in women. The mean weight gain from baseline to 12 months after the end of SCT was 0.9 kg ($SD = 3.9$ kg) in men and 1.7 kg ($SD = 3.6$ kg) in women.

Figure 2 shows the cross-sectional change in body weight from baseline to the second through fifth sessions in the SCT and 3, 6, and 12 months after the end of SCT. The proportion of those with marked weight gain of ≥3.5 kg increased over time both during the SCT (0%–16.2%) and after the end of SCT (17.7%–25.8%).

Comparison of Weight Gain Groups

Subjects aged 49 years and younger showed higher weight gain than the older group ($p = 0.084$; Table 2). Participants who had a comorbidity with nicotine dependence tended to be divided into two groups: those in whom the weight increased sharply and those in whom the weight decreased sharply, compared with those who had no disease. Those who had a high

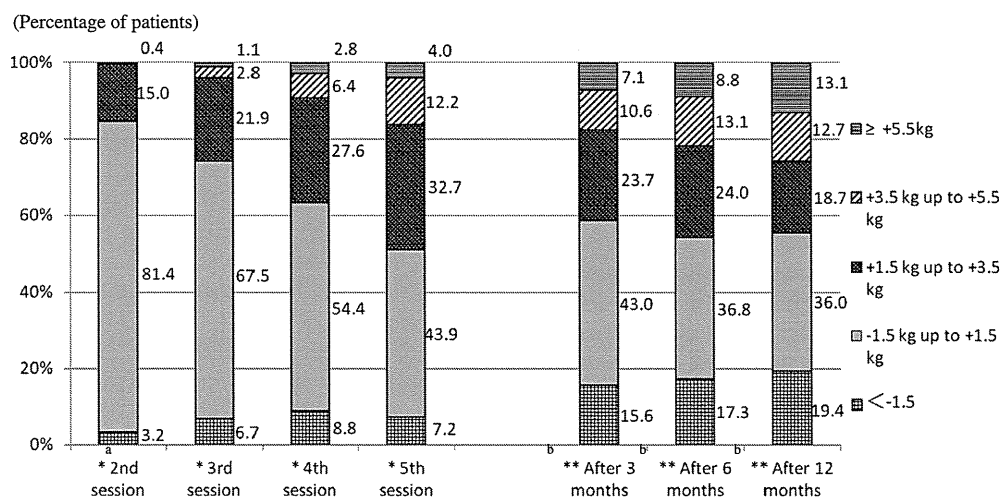

FIGURE 2. Changes in body weight between baseline and 12 months after the end of smoking cessation therapy among the study subjects ($N = 283$). [a]Second session: 2 weeks after the first session; third session: 4 weeks after the first session; fourth session: 8 weeks after the first session; fifth session: 12 weeks after the first session. [b]After *x* months from the end of smoking cessation therapy.

TABLE 2. Weight Change From Baseline to 12 Months After the End of Smoking Cessation Therapy by Potential Risk Factors

			Weight change (kg)					
Potential risk factor	Group	*n*	<−1.5	−1.5 to <1.5	1.5 to <3.5	3.5 to <5.5[a]	≥5.5kg[a]	*p*[b]
Sex	Female	83	19.3	26.5	25.3	13.3	15.7	.17
	Male	200	19.5	40.0	16.0	12.5	12.0	
Age (years)	<50	87	18.4	32.2	13.8	13.8	21.8	.08
	≥50	196	19.9	37.8	20.9	12.2	9.2	
Comorbidity	Absence		11.8	41.2	29.4	8.8	8.8	.83
	Presence		20.5	35.3	17.3	13.3	13.6	
BMI	<25		15.0	40.2	17.5	13.4	13.9	.14
	≥25		29.2	27.0	21.4	11.2	11.2	
FTND score	≥7	109	18.4	29.4	18.4	16.5	17.4	.04
	<7	174	20.1	40.2	19.0	10.3	10.3	
Number of cigarettes per day	≥30	98	20.4	30.6	20.4	18.4	10.2	.66
	<30	185	18.9	38.9	17.8	9.7	14.6	
Prescription	Varenicline	249	20.1	36.6	19.3	12.5	11.7	.08
	Nicotine patch	32	12.5	34.4	12.5	15.6	25	
Nausea	Positive	79	21.5	40.5	16.5	10.1	11.4	.22
	Negative	196	18.9	34.2	18.9	13.8	14.3	
Craving (at the end of SCT)	Negative	162	21.0	38.9	18.5	8.6	13.0	.03
	Positive	78	14.1	30.8	20.5	19.2	15.4	
Smoking status (at the end of SCT)	Quitters	234	16.2	35.0	21.4	14.1	13.3	.01
	Smokers	49	34.7	40.8	6.1	6.1	12.2	
Smoking status (after 12 months)	Quitters	194	17.0	32.5	20.1	13.9	16.5	.01
	Smokers	89	24.7	43.8	15.7	10.1	5.6	

Note. $N = 283$. Cell entries are percentages in groups. FTND = Fagerström Test for Nicotine Dependence.
[a]Participants who had marked weight gain (3.5 kg and over).
[b]Mann–Whitney *U* test.

degree of nicotine dependence (FTND ≥ 7) revealed significantly increased body weight compared with patients with low nicotine dependence (FTND < 7; $p = .04$). Varenicline users showed lower weight gain compared with nicotine patch users, but it was not statistically significant ($p = .08$). Participants who had still felt craving at the end of SCT had a significant body weight increase compared with the no-craving group ($p = .001$). The subjects who succeeded in quitting smoking at 12 months after the end of SCT had significantly higher weight gain than those who did not ($p = .002$; Table 2).

In addition, the relationship between nausea, a prevalent side effect of varenicline, and weight gain (in kilograms) at the end of SCT in the 249 varenicline users were examined. Twenty-nine percent of varenicline users had nausea, which showed an inverse correlation with weight gain ($p = .06$).

Factors Associated With Weight Gain

At the End of SCT In stepwise regression analysis with weight gain of +3.5 kg at the end of SCT as a dependent variable, significant associations were observed in FTND score (being ≥7: *OR* = 2.31, 95% CI [1.15, 4.64]) and smoking status at the end of SCT (quitters: *OR* = 10.91, 95% CI [1.42, 83.69]; Table 3). Varenicline users had lower risk of weight gain than nicotine patch users, although it was statistically insignificant (*OR* = 0.40, $p = .08$).

At 12 Months After Completion of SCT Subsequently, a stepwise regression analysis with weight gain of +3.5 kg or more at 12 months after the end of SCT was investigated as a dependent variable. Age 50 years and over (*OR* = 0.38, 95% CI [0.19, 0.76]) and varenicline use (*OR* = 0.30, 95% CI [0.11, 0.78]) were significantly associated with lower weight gain (Table 4). The presence of a comorbidity with nicotine dependence (*OR* = 3.33, 95% CI [1.10, 10.00]), high FTND score (≥7) at baseline (*OR* = 2.07, 95% CI [1.09, 3.92]), and success in quitting smoking at 12 months after the end of SCT (*OR* = 4.57, 95% CI [1.94, 10.08]) were significant risk factors for marked weight gain (Table 4).

Discussion

In this study, factors associated with increasing body weight in patients who received SCT provided by the Japanese medical

TABLE 3. Factors Associated With Marked Weight Gain (Baseline to End of Smoking Cessation Therapy)

Factor	Group	*OR*	*p*	95% CI
FTND	<7	1.00[a]		
	≥7	2.31	.02	[1.15, 4.64]
Prescription	Nicotine patch	1.00[a]		
	Varenicline	0.40	.08	[0.15, 1.12]
Smoking status	Smokers	1.00[a]		
	Quitters	10.91	.02	[1.42, 83.69]

Note. $N = 283$. Stepwise logistic regression analysis. Nonsignificant factors included in the analysis were gender, age, comorbidity, body mass index, nicotine dependence, number of cigarettes smoked per day, prescription, craving, and smoking at the last session. *OR* = odds ration; CI = confidence interval; FTND = Fagerström Test for Nicotine Dependence.
[a]Reference group.

insurance system were investigated. The findings showed that weight gain of 3.5 kg and over, at the end of SCT, were significantly associated with high FTND score at the initiation of SCT and success in quitting smoking at the end of SCT. In addition, weight gain of 3.5 kg and over at 12 months after the end of SCT was significantly associated with age lower than 50 years old, presence of a comorbidity with nicotine dependence, high FTND score at the initiation of SCT, non-varenicline use, and success in quitting smoking at 12 months after the end of SCT. The average weight gain from baseline to 12 months after the end of SCT was 1.2 kg.

Factors Associated With Weight Gain

High-Nicotine Dependence In this study, nicotine dependence (FTND score ≥ 7) at baseline was significantly associated with weight gain. The FTND was not administered in previous studies (Klesges et al., 1997; Levine et al., 2013; Williamson et al., 1991); instead, nicotine addiction had only been assessed using the proxy measure of number of cigarettes smoked per day. The FTND includes the number of cigarettes smoked per day in the questionnaire items. Therefore, the variable of the number of cigarettes smoked per day was thought to be automatically excluded by stepwise regression analysis because of overadjustment. If someone had strong FTND-oriented nicotine dependence, he or she would readily develop nicotine withdrawal symptoms in a smoking cessation program. Withdrawal symptoms of nicotine induce hunger and weight gain (Klesges et al., 1995; West, Hajek, & Belcher, 1989; Zaniewska, Przegalinski, & Filip, 2009). Thus, the participants who had a high FTND score would also be at high risk of weight gain. From this result, it was considered that the FTND score is able to be used as a factor that predicts weight gain in Japanese SCT patients.

Smoking Status The study revealed that those who stopped smoking for at least 2 weeks at the end of SCT had 10.9 times higher risk of weight gain from baseline to the end of SCT than those who failed to stop smoking. The impact of smoking cessation on weight gain seemed to be attenuated according to the length of time elapsed; the odds ratio decreased to 4.6 at 12 months after the end of SCT. These findings may be plausible in that, over a long duration (approximately 12 months), the impact of other lifestyle factors besides smoking behavior on weight gain becomes relatively important.

Prescription Varenicline users had lower risk of weight gain than nicotine patch users at 12 months after the end of SCT (*OR* = 0.30, 95% CI [0.11, 0.78]). The recently published Cochrane review showed that the difference in mean weight change at the end of smoking cessation intervention between varenicline and nicotine patch users was −0.05 kg, and it was not significant (Farley, Hajek, Lycett, & Aveyard, 2012). In a meta-analysis of weight gain, the increase in body weight at 12 months after smoking cessation intervention was 4.9 kg in the nicotine replacement therapy group and 4.2 kg in the varenicline group, which were not significantly different (Aubin et al., 2012). In the study, nausea, a prevalent side effect of varenicline, occurred in 29% of varenicline users. Experiencing nausea during the period of SCT showed an inverse correlation with weight gain at the end of SCT ($p = .06$). Nausea occurring in patients who take varenicline might suppress weight gain through decreased appetite. In addition, termination of the nicotine patch sometimes leads to craving of smoking, which might induce rapid weight gain because of increasing appetite (Klesges et al., 1995). In Japan, the standard prescription period is 12 weeks for varenicline and 8 weeks for nicotine patch. This difference might also be attributed to the relatively stronger weight gain suppression in varenicline users.

TABLE 4. Factors Associated With Marked Weight Gain (Baseline to 12 Months After the End of Smoking Cessation Therapy)

Factor	Group	*OR*	*p*	95% CI
Age (years)	<50	1.00[a]		
	≥50	0.38	.01	[0.19, 0.76]
Comorbidity	Absence	1.00[a]		
	Presence	3.33	.03	[1.10, 10.00]
FTND	<7	1.00[a]		
	≥7	2.07	.03	[1.09, 3.92]
Prescription	Nicotine patch	1.00[a]		
	Varenicline	0.30	.01	[0.11, 0.78]
Smoking status	Smokers	1.00[a]		
	Quitters	4.57	.01	[1.94, 10.08]

Note. $N = 283$. Stepwise logistic regression analysis. Nonsignificant factors included in the analysis were gender, BMI, number of cigarettes smoked per day, nausea, and craving. *OR* = odds ratio; CI = confidence interval; FTND = Fagerström Test for Nicotine Dependence; BMI = body mass index.
[a]Reference group.

Comorbidity With Nicotine Dependence Contrary to expectation, participants who had a comorbidity with nicotine dependence had a higher risk of marked weight gain compared with those who had no comorbidity. In this study, participants who had a comorbidity with nicotine dependence showed bipolarization to those whose weight increased sharply and those whose weight decreased sharply, compared to those who had no other disease. It seems that higher weight gain may have reflected both the effect of smoking cessation and the effect of physical response to medical treatment of the underlying disease.

Weight Change The postcessation weight gain observed in this study was relatively small compared with the postcessation weight gain in other studies of changing smoking behavior that were reported in Western countries (Aubin et al., 2012; Klesges et al., 1997; O'Hara et al., 1998; Williamson et al., 1991). One observation in Japan reported that the mean weight gain in 18 months of continuous quitters was 3.5 kg (*SD* = 2.7 kg), although the study did not clarify factors associated with the risk of weight gain (Kadowaki et al., 2006). A plausible explanation for the lower weight gain in Japanese is that the traditional low-fat Japanese diet and smaller body size would contribute to the relatively smaller weight gain.

Strengths and Limitations

A strength of this study was that the impact of various factors important to smoking cessation on post-cessation treatment weight gain were investigated quantitatively. In addition, as many as seven sequential time points for weight change during and after termination of SCT were observed. Also, to the best of our knowledge, this is the first study to focus on investigation of factors associated with weight gain in Asian individuals who received smoking intervention. A potential limitation of our study was the use of self-reports to assess smoking status and body weight at the follow-up surveys. This may have resulted in an inaccurate record by the study subjects.

Conclusion

The study showed that a high nicotine dependence at the start of SCT, non-varenicline use, presence of a comorbidity, and successfully quitting smoking were significantly associated with marked weight gain among persons who received SCT in Japan. Further studies are needed to validate these associations and elucidate other factors for the risk assessment of weight gain during smoking cessation interventions among the Asian population. ▼

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特集 肺がんの薬物療法―最近の進歩

MEK阻害薬の展望*

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Key Words：MEK inhibitor, MAP kinase cascade, *KRAS/BRAF* mutation

はじめに

2002年にゲフィチニブが臨床導入されて以来，さまざまな新規分子標的薬が開発されてきているが，肺がんにおいて新たに一般臨床に導入された分子標的薬はベバシズマブのみである．肺がん領域において承認されているMEK(MAPK kinase, MAPKK)阻害薬はなく，開発中の薬剤について解説する．

MAPキナーゼ・カスケード

MAPキナーゼ(mitogen-activated protein kinase, MAPK/ERK)カスケードは細胞の増殖，分化，死，ストレス応答など多くの細胞機能の制御にかかわり，酵母から高等植物や哺乳動物に至るまで高度に保存された細胞内シグナル伝達経路である．MEKは，細胞内シグナル伝達経路の一つであるMAPキナーゼ・カスケードのシグナル伝達を制御する重要な酵素であり，Ras, Rafの下流に位置する．MAPキナーゼの活性化にはそのリン酸化が必要であり，MEKによってスレオニン残基(T)とチロシン残基(Y)がリン酸化される．MEKはその上流のMEKキナーゼによってリン酸化を受けることで活性化される．このように細胞内シグナル伝達経路がMEKキナーゼ→MEK→MAPキナーゼといった滝のように進むことから，MAPキナーゼ・カスケードと呼ばれている(図1)．上皮細胞増殖因子などの増殖因子がチロシンキナーゼ型受容体に結合すると低分子G蛋白質RasがGTP結合型になり，MEKキナーゼであるRafを活性化することでMAPカスケードが動き出す，このカスケードは，*BRAF*や*RAS*遺伝子変異などにより多くの腫瘍で活性化されており[1)~3)]，MEKを阻害することにより，マウスのゼノグラフトモデルでヒトの腫瘍の増殖を阻害することが示されている[4)]．

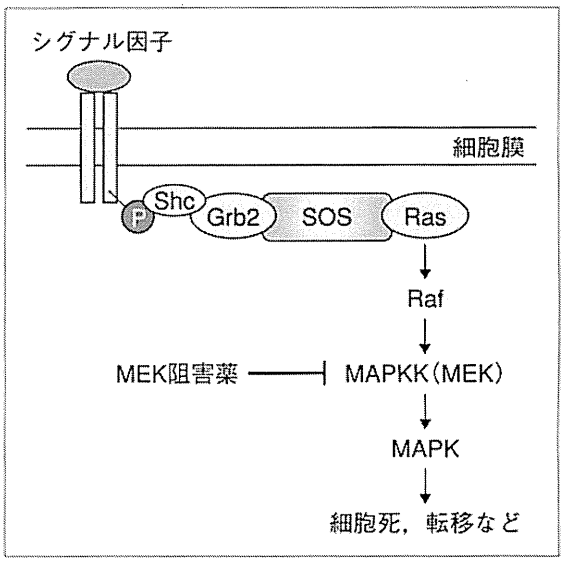

図1　MAPキナーゼ・カスケード

* Prospect of MEK inhibitor.

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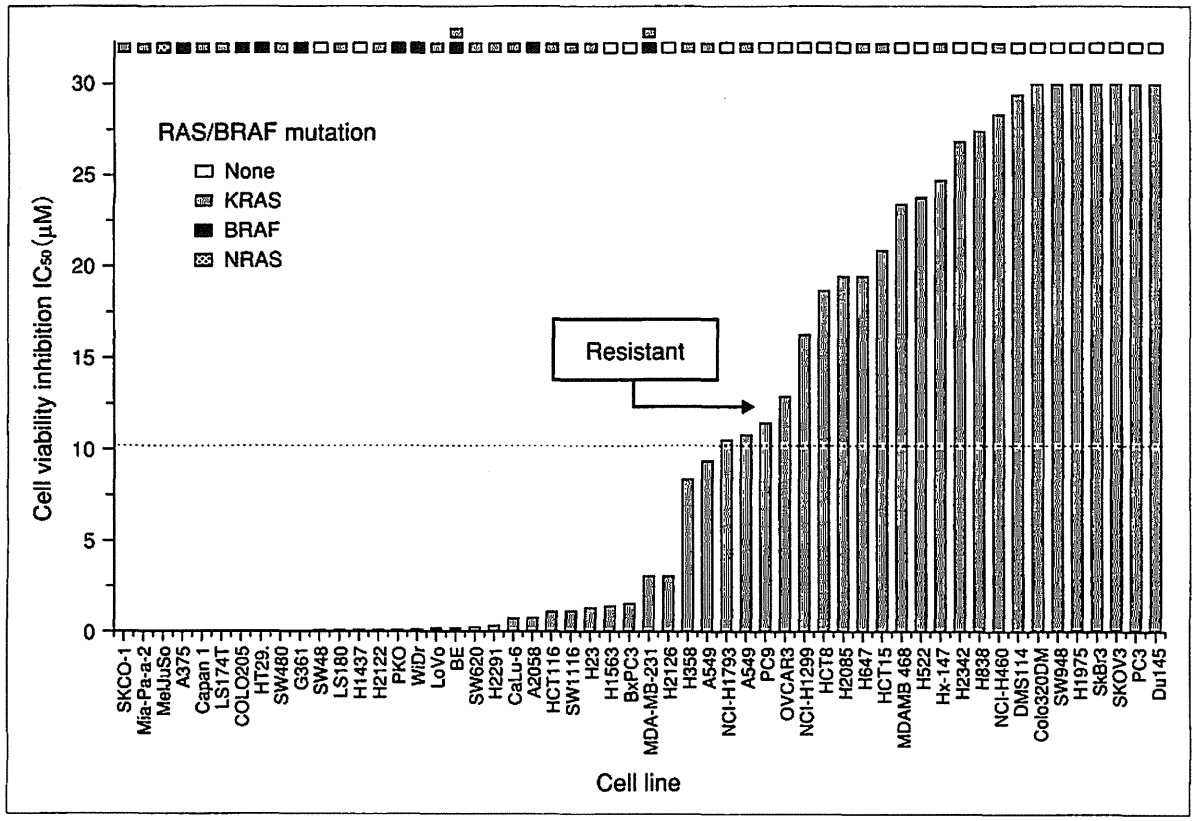

図2　セルラインにおけるAZD6244の感受性（文献[5]より引用）

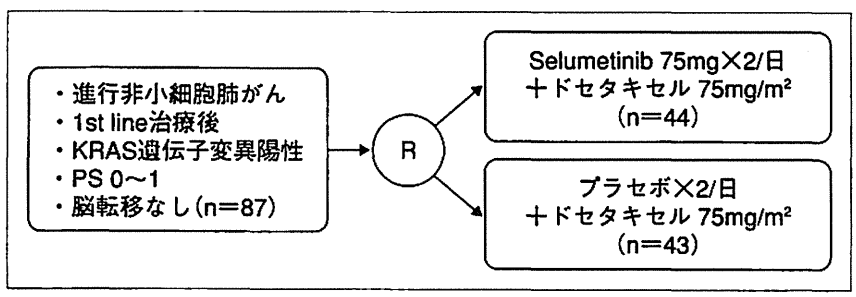

図3　ドセタキセル±selumetinib試験スキーム

MEK阻害薬

1．AZD6244（selumetinib）

強力かつ選択的にMEK 1/MEK 2 のATPを非競合的に阻害する経口薬であり，*KRAS/BRAF*遺伝子変異を有する細胞株で感受性が高いことが報告されている（図2）[5]．パートAとBに分けて第Ⅰ相試験が行われ，パートAで最大耐用量（maximum tolerated dose；MTD）の決定，パートBでは新規に開発されたカプセル剤と従来の内用液剤との薬物動態，薬力学，臨床効果の比較を行った[6]．パートAに30例が登録され，カプセル剤のMTDは75mg×2/日であった．容量制限毒性（dose limiting toxicities；DLT）はgrade 3（CTC-AE ver. 3.0）のざ瘡様皮疹と胸水であった．MTDで最も頻度の高かった有害反応は，疲労（65.7％）とざ瘡様皮疹（60.0％）であった．パートBにおいてカプセル剤75mgと内用液剤100mgとの相対的バイオアベイラビリティが評価された．薬物血中濃度時間曲線下面積（area under the blood concentration time curve；AUC）$_{0\text{-}24}$に基づく相対的バイオアベイラビィティは197％（90％信頼区間：161～242％であった）．

マウスモデルを用いてAZD6244とドセタキセ

表1　ドセタキセル±selumetinib試験の患者背景

	Selumetinib +DOC	プラセボ +DOC
Male/Female	21/23	20/23
Age, median(range)	59.5(26～79)	59(37～76)
Smoking status		
Former, current	39	38
Never	5	5
IIIB/IV	5/39	1/42
PS 0/1	21/23	21/22
Histological type		
Ad	36	33
Sq	3	6
Ad-Sq	2	1
Large	2	0
Others	1	3

DOC：docetaxel，PS：performance status，Ad：adenocarcinoma，Sq：squamous．(文献[9]より引用)

ルとの併用効果を検討した結果，各薬剤の単剤よりも併用することにより効果の上乗せが認められた[7]．さらに，AZD6244とドセタキセル併用の第I相試験が行われ，AZD6244の推奨容量は75mg×2/日であった[8]．

*KRAS*遺伝子変異陽性の進行非小細胞肺がんを対象とした二次治療としてのドセタキセルにselumetinibの上乗せ効果を検討した無作為化第II相試験がAmerican Society of Clinical Oncology (ASCO) Annual Meeting 2012で報告された[9]．対象症例は，全身状態(performance status；PS)0～1，*KRAS*遺伝子変異陽性の進行非小細胞肺がんで，一次治療後に進行した症例であった．この試験はドセタキセル75mg/m^2＋プラセボを対照群，ドセタキセル75mg/m^2＋selumetinib75mg×2/日を試験治療群とし，主要評価項目を全生存期間として行われた．全87例のうち対照群43例，試験治療群44例と1対1に割り付けられた(図3)．患者背景として，男女比はほぼ1対1，年齢中央値が約60歳，非喫煙者が11%，腺がんが約80%を占めていた(表1)．*KRAS*遺伝子変異の型はこれまでの報告とほぼ同様であった[10]．ドセタキセルの治療サイクル中央値は，対照群が4，試験治療群が5であり，selumetinibの投与中央値は117日であった．主要評価項目である生存期間中央値は，対照群5.2か月，試験治療群9.4か月，HR 0.80(80%信頼区間：0.56～1.14，P=0.2069)であり，有意な生存期間の延長は認めなかった(図4)．無増悪生存期間は，対照群2.1か月，試験治療群5.3か月，HR 0.58(80%信頼区間：0.42～0.79，P=0.0138)と有意な改善を認めた(図4)．奏効割合は，対照群が0%，試験治療群が37.2%であった(図5)．主要評価項目は達成されなかったものの，奏効割合，無増悪生存期間で有意な改善を認めており，今後の臨床開発が期待される．

2．trametinib

可逆性なMEK1/MEK2選択的阻害薬である．In-vitroの研究では，*BRAF*遺伝子変異陽性のセルラインに対し7/10で殺細胞性の効果を示し，*RAS*遺伝子変異陽性のマウスゼノグラフトモデルとセルラインにおいても効果的であった．これを受けて，進行固形がんに対し第I相試験が行われた[11]．206例が登録され，非小細胞肺がんは30例(15%)であった．MTDは3 mg/日であり，第II相試験の推奨投与量は2 mg/日であった．最も頻度の高い有害反応は皮疹(165例，80%)と下痢(87例，42%)であり，ほとんどがグレード2以下であった．DLTとなった毒性は皮疹(2例)，下痢(1例)，中心性漿液性網膜症(2例)であった．非小細胞肺がんのうち2例が部分奏効(partial response；PR)であり，*KRAS*，*BRAF*遺伝子変異陽性例であった．

3．RO4987655

高度選択的アデノシン3リン酸非競合的な経口MEK阻害薬である．進行固形がんに対しての第I相試験が報告されている[12]．49例が登録され，肺がんは3例であった．MTDは8.5mg×2回/日であった．DLTは霧視が1例，クレアチンキナーゼ(creatine kinase；CK)上昇が3例であった．最も頻度の高い有害反応は皮疹(91.8%)，胃腸障害(69.4%)であった．半減期はほぼ4時間であった．評価可能であった症例38例のうち8例(21.1%)で臨床的な有用性を示し，2例でPRを得た．今後は*RAS/RAF*遺伝子変異を持つ腫瘍に対し開発を進める予定である．

おわりに

MEK阻害薬は，*RAS/RAF*遺伝子変異陽性を持つ腫瘍を対象に開発が進められているのが現状