学位論文

(Pro)renin Receptor Down-regulation Is Associated With a Higher Risk of Recurrence in Lung Adenocarcinoma

香川大学大学院医学系研究科

医学専攻

木村なちの

ANTICANCER RESEARCH *43*: 5671-5680 (2023)
doi:10.21873/anticanres.16772

(Pro)renin Receptor Down-regulation Is Associated With a Higher Risk of Recurrence in Lung Adenocarcinoma

NACHINO KIMURA[1], KYUICHI KADOTA[2], EMI IBUKI[1], RYOU ISHIKAWA[1], TOSHIHIRO IKEDA[3], CHIHIRO YOSHIDA[3,4], TOSHIKI YAJIMA[3], AKIRA NISHIYAMA[5] and REIJI HABA[1]

[1]*Department of Diagnostic Pathology, Faculty of Medicine, Kagawa University, Kagawa, Japan;*
[2]*Department of Molecular Oncologic Pathology, Faculty of Medicine, Kagawa University, Kagawa, Japan;*
[3]*Department of General Thoracic Surgery, Faculty of Medicine, Kagawa University, Kagawa, Japan;*
[4]*Department of General Thoracic Surgery, Kochi Health Sciences Center, Kochi, Japan;*
[5]*Department of Pharmacology, Faculty of Medicine, Kagawa University, Kagawa, Japan*

Abstract. *Background/Aim: The (pro)renin receptor [(P)RR] plays a role not only in cardiovascular and renal diseases, but also in tumorigenesis. (P)RR contributes to the activation of the Wnt/β-catenin signaling pathway, independent of the renin-angiotensin system. Accumulating evidence has shown that (P)RR is expressed in various human cancers. However, its clinical impact in lung carcinomas remains unclear. This study aimed to clarify the associations between (P)RR expression and clinical outcomes in patients with non-small cell lung carcinoma (NSCLC). Patients and Methods: We analyzed the data of 913 patients with NSCLC who underwent resection between 1999 and 2016. Tissue microarrays were constructed and the expression of (P)RR and β-catenin was investigated using immunohistochemistry. Recurrence-free probability and overall survival were analyzed using a log-rank test and Cox proportional hazards model. Results: In adenocarcinomas, (P)RR down-regulation correlated significantly with high-grade tumors (p=0.026) and a higher risk of recurrence in all patients (p=0.001). Among patients with (P)RR-positive tumors, the nuclear expression of β-catenin was associated with a higher risk of recurrence (p=0.001). Multivariate analysis revealed that (P)RR down-regulation was an independent predictor of disease recurrence (p=0.031). Conversely, in squamous cell carcinoma, (P)RR was not associated with patient outcomes. Conclusion: (P)RR down-regulation is associated with a higher risk of recurrence in lung adenocarcinomas, thereby characterizing a prognostic subset within high-grade tumors.*

Correspondence to: Kyuichi Kadota, MD, Department of Molecular Oncologic Pathology, Faculty of Medicine, Kagawa University, 1750-1, Ikenobe, Miki-cho, Kita-gun, Kagawa 761-0793, Japan. Tel: +81 878982111, Fax: +81 878912112, e-mail: kadota.kyuichi@kagawa-u.ac.jp

Key Words: Lung cancer, (Pro)renin receptor, adenocarcinoma.

The (pro)renin receptor [(P)RR] is a single transmembrane domain protein consisting of 350 amino acids (1). It plays important roles in various pathways, including those of vacuolar H^+-ATPase (V-ATPase), Wnt/β-catenin, the renin-angiotensin system (RAS), MAPK/ERK, and PI3K/AKT/mTOR. (P)RR plays important roles in cardiovascular and renal physiological function and disease, and has recently been associated with a range of physiological and pathological processes, including tumorigenesis (2-11). (P)RR is over-expressed in colorectal cancer, breast cancer, pancreatic ductal adenocarcinoma, glioblastoma, and aldosterone-producing adenoma (12-16). Similarly, the Wnt/β-catenin pathway is known to contribute to the development of various cancers, including colorectal, gastric, breast, and adrenocortical cancer (17-20). Recent studies have shown that (P)RR promotes the development of colorectal cancer, pancreatic ductal carcinoma, and glioma through the Wnt/β-catenin pathway (12, 14, 15).

(P)RR regulates lung development *via* the Wnt/β-catenin signaling pathway (21). The Wnt signaling pathway is important for the development of non-small cell lung cancer (22). The relationship between (P)RR and β-catenin has been reported in the development of some tumors; however, this relationship and the prognostic value of (P)RR remain unclear in non-small cell lung carcinoma. In this study, we investigated (P)RR and β-catenin expression and the potential prognostic role of (P)RR in a cohort of Japanese patients with therapy-naive lung adenocarcinoma and squamous cell carcinoma who underwent surgery.

Patients and Methods

Patients. This retrospective study was approved by the Institutional Review Board of Kagawa University (23). We collected data for patients with therapy-naive lung adenocarcinoma and squamous cell carcinoma who underwent surgical resection at Kagawa University between April 1, 1999 and December 31, 2016 (n=1,020). Patients were staged using the 8th edition of the American Joint Committee

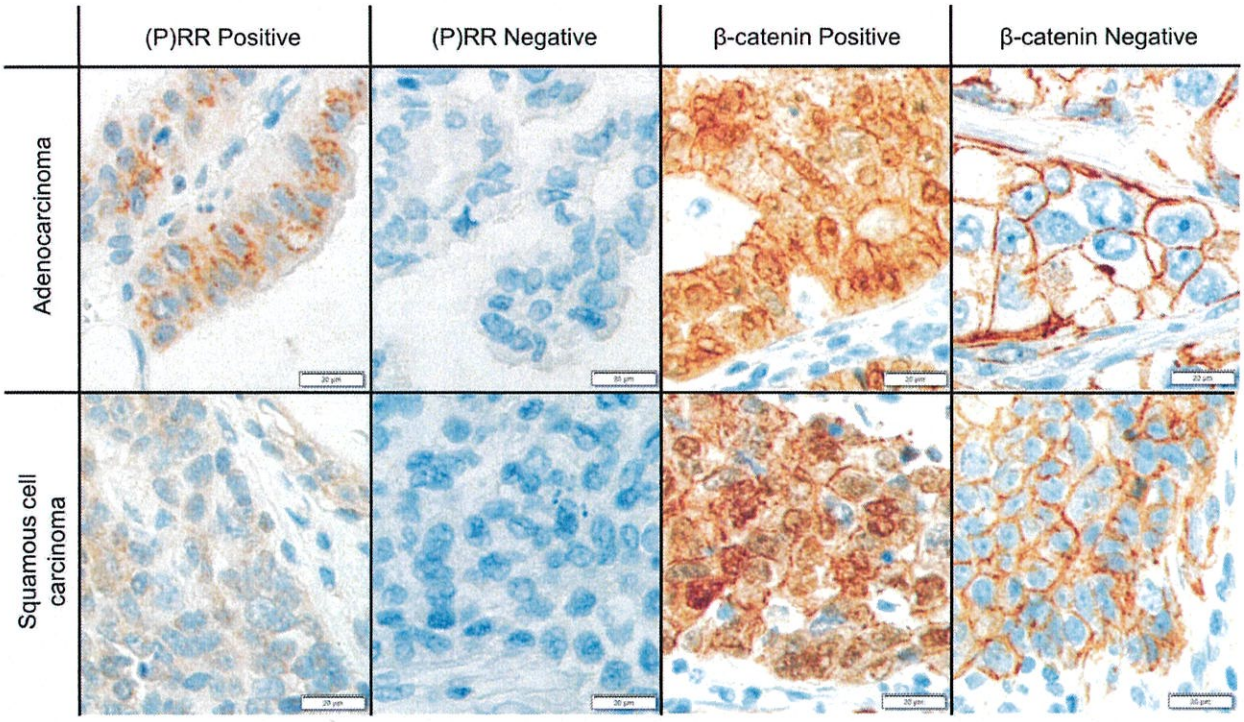

Figure 1. *Immunohistochemistry for (pro)renin receptor [(P)RR] and β-catenin. The upper row shows images of adenocarcinoma and the lower row shows images of squamous cell carcinoma. Scale bar: 20 μm.*

on Cancer TNM Staging Manual. Subsets of the cases in this study have been used in our previous publications, and we applied the same patient inclusion criteria for this study (23).

Histologic evaluation. Two pathologists blinded to clinical outcomes of the patients reviewed the hematoxylin & eosin (H&E) stained slides using an Olympus BX53 upright microscope (Olympus, Tokyo, Japan) with a standard 22-mm-in-diameter eyepiece.

Tumors were classified into histological subtypes and graded into Grade1, 2, or 3, according to the 2021 WHO classification of lung carcinomas. A high-grade pattern (solid, micropapillary, cribriform, or complex glandular pattern) was considered to be present when the tumor consisted of 5% or more high-grade pattern. Lymphatic or vascular invasion and spread through air space (STAS) were defined as previously described (24).

Immunohistochemistry of microarray specimens. Tissue microarrays were used as described in our previous publications (23, 24). In total, 913 of the 1,020 cases had sufficient core samples for immunohistochemical analysis.

We prepared 4-μm sections from the tissue microarray blocks and stained them with anti-human (P)RR rabbit polyclonal antibody (15, 25), using a Bench Mark ULTRA automated immunohistochemical slide staining system (Ventana Medical Systems, Tucson, AZ, USA). Diaminobenzidine was used as the chromogen and hematoxylin was used as the nuclear counterstain. The positive control tissues were stained in parallel with the study cases.

We assessed the cytoplasmic expression of (P)RR in the tumor cells. Cytoplasmic (P)RR staining was scored as 0 (no expression), 1 (mild expression), 2 (intermediate expression), or 3 (strong expression). When the score was equal to or higher than the median, expression was classified as positive (Figure 1).

Based on tissue microarray analysis, the immunohistochemical results of β-catenin nuclear expression were obtained from our previous study (24) (Figure 1).

Statistical analysis. All analyses were performed using SPSS Statistics for Windows (version 23.0; IBM SPSS, Armonk, NY, USA). Associations between variables were analyzed using the chi-squared test for categorical variables. Recurrence-free probability (RFP) and overall survival (OS) were defined and statistically analyzed as previously described (23, 24). Multivariate analyses were performed using a Cox proportional hazards regression model and its models were built according to our previous publications (23, 24). All statistical tests were two-sided and $p<0.05$ was considered significant.

Results

Clinicopathological characteristics of patients. A total of 913 patients were included: 686 with adenocarcinoma and 227 with squamous cell carcinoma. Among the patients with adenocarcinoma, the mean age was 69 years (range=26-92

years). Nearly half of the patients were male (n=367), and most patients were Stage 0-I (n=552). Of these, 124 were lost, and 141 experienced recurrence. The median follow-up for survivors was 62.1 months [mean±standard deviation (SD)=69.4±37.5]. The mean age of patients with squamous cell carcinoma was 73 years (range=41-88 years). Most patients were male (n=214), and more than half of the patients were Stage 0-1 (n=140). Of these, 95 were lost, and 57 experienced recurrence. The median follow-up for survivors was 52.5 months (mean±SD, 58.4±42.4).

(P)RR expression is associated with some clinicopathological features and nuclear β-catenin expression. In adenocarcinoma, the (P)RR expression score was 0 in 95 patients, 1 in 478 patients, 2 in 98 patients, and 3 in 15 patients. The median and cut-off were 1, distinguishing the group that were fully negative and those that showed some expression (positive). Most patients were positive, with nearly 80% of the (P)RR-positive patients scoring 1 (Figure 2A). Patients with IASLC Grade 3 adenocarcinoma were also mostly positive (Figure 2B). STAS was more frequently observed in (P)RR-negative adenocarcinomas than in (P)RR-positive adenocarcinomas (p=0.019). A high-grade pattern was also more often present in (P)RR-negative adenocarcinomas than in (P)RR-positive adenocarcinomas (p=0.002); however, no relationship was observed between (P)RR and IASLC grade (Table I).

Regarding (P)RR expression in squamous cell carcinoma, 99 patients had a score of 0, 123 had a score of 1, 4 had a score of 2, and 1 had a score of 3 (Figure 2C). Similar to adenocarcinoma, squamous cell carcinoma had a median and cut-off of 1, distinguishing positive and negative groups. In patients with squamous cell carcinoma, nuclear β-catenin was detected more frequently in (P)RR-positive squamous cell carcinomas (p=0.003). Pathological stage was associated with (P)RR (p=0.012; Table II).

Association between (P)RR expression and patient outcome. For adenocarcinomas, the 5-year RFP rate was significantly shorter in (P)RR-negative patients than in (P)RR-positive patients (negative: 68%, positive: 80%; p=0.001; Figure 3A). The 5-year OS rate was also shorter in negative patients than in positive patients, but the difference was not significant (negative: 80%, positive: 84%; p=0.064; Figure 3B). Among (P)RR-positive patients, β-catenin-positive patients had significantly worse 5-year RFP and OS than β-catenin-negative patients (5-year RFP, p=0.001; 5-year OS, p=0.001; Figure 3C and D). A similar trend was observed in Kaplan–Meier analysis of patients with IASLC Grade 3 (Figure 4).

Multivariate analysis of RFP for adenocarcinoma (adjusted for pathological stage, STAS, lymphovascular invasion, (P)RR, and nuclear β-catenin expression) showed that (P)RR remained independently associated with a lower risk of adenocarcinoma recurrence (HR=0.64, p=0.031); however, β-catenin expression was not an independent predictor of adenocarcinoma recurrence (HR=1.30, p=0.193; Table III).

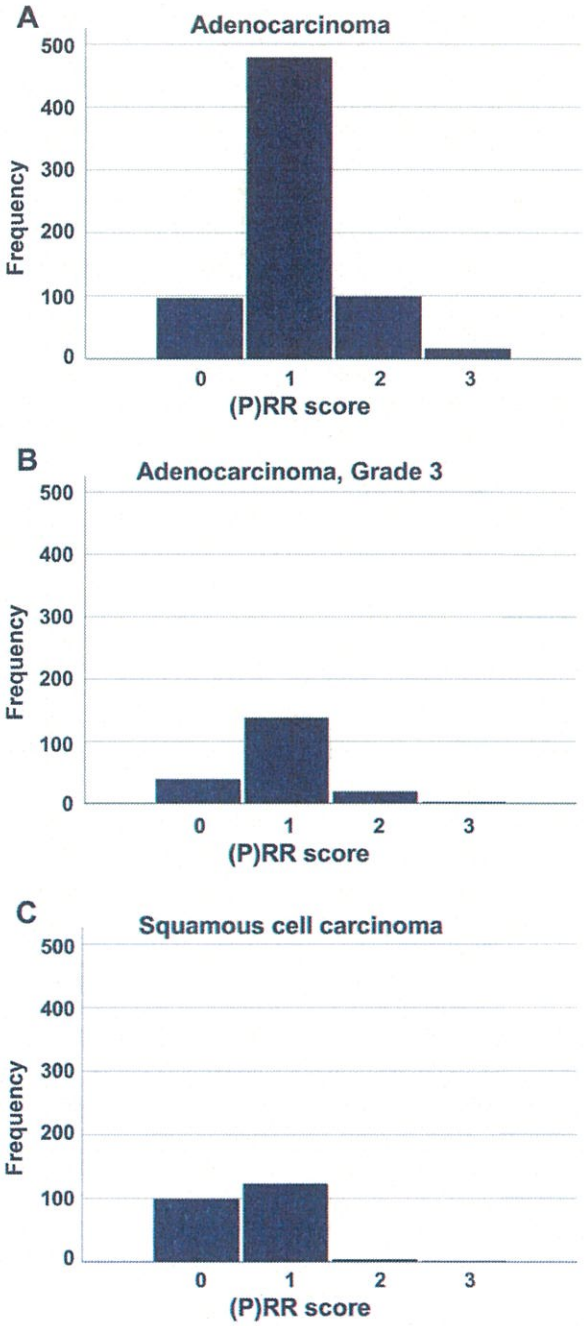

Figure 2. *(Pro)renin receptor [(P)RR] scoring. Frequency of patients with (A) adenocarcinoma, (B) IASLC Grade 3 adenocarcinoma, or (C) squamous cell carcinoma.*

In squamous cell carcinoma, (P)RR-positive and (P)RR-negative patients showed no difference regarding either 5-

Table I. *Association of (pro)renin receptor [(P)RR] expression with clinicopathological features and nuclear β-catenin expression in adenocarcinoma.*

Variables	N	(P)RR expression				*p*-Value
		Negative	(%)	Positive	(%)	
Sex						0.481
Female	319	41	(13)	278	(87)	
Male	367	54	(15)	313	(85)	
Age						0.150
≤65	230	38	(17)	192	(83)	
>65	456	57	(13)	399	(87)	
Pathological stage						0.253
0	33	4	(12)	29	(88)	
I	519	66	(13)	453	(87)	
II	58	9	(16)	49	(84)	
III	76	16	(21)	60	(79)	
STAS						**0.019**
Absent	428	49	(11)	379	(89)	
Present	258	46	(18)	212	(82)	
Lymphovascular invasion						0.269
Absent	425	54	(13)	371	(87)	
Present	261	41	(16)	220	(84)	
Nuclear β-catenin						0.874
Negative	265	36	(14)	229	(86)	
Positive	421	59	(14)	362	(86)	
IASLC grade						0.077
Grade 1	81	10	(12)	71	(88)	
Grade 2	228	28	(12)	200	(88)	
Grade 3	198	39	(20)	159	(80)	
Presence of high-grade pattern						**0.002**
Absent	401	42	(10)	359	(90)	
Present	285	53	(19)	232	(81)	

STAS: Spread through air space; IASLC: International Association for the Study of Lung Cancer. Significant *p*-values are shown in bold.

year RFP or OS (5-year RFP, p=0.301; 5-year OS, p=0.702). Among (P)RR-positive patients, there was no significant difference between β-catenin-positive and -negative expression regarding either 5-year RFP or OS (5-year RFP, p=0.410; 5-year OS, p=0.347; Figure 5).

Discussion

In this study, we performed a series of immunohistochemical analyses to determine the prognostic relevance of (P)RR and its relationship with β-catenin activity. We examined the specimens and data of a large cohort of patients with therapy-naive lung adenocarcinoma and squamous cell carcinoma who underwent lobectomy or more limited resection at a single institution. We evaluated (P)RR expression simply as positive or completely negative, and found that most cases showed positive expression. Although the role of (P)RR in lung cancer is unknown, the down-regulation of (P)RR may have some implications in its pathogenesis. In adenocarcinoma, the down-regulation of (P)RR expression was associated with STAS and the presence of a high-grade pattern. There was also a higher risk of recurrence in (P)RR-negative adenocarcinoma patients. Patients with IASLC Grade 3 adenocarcinomas showed an association between (P)RR-negative expression and a higher risk of recurrence. In patients with (P)RR-positive adenocarcinoma, the nuclear accumulation of β-catenin was associated with a poor prognosis. In squamous cell carcinoma, there was no correlation with poor prognosis.

Wang *et al.* reported that colorectal cancer patients with stronger (P)RR expression had shorter recurrence-free survival times (12). Larrinaga *et al.* showed that intense immunohistochemical positivity of (P)RR in invasive urothelial carcinoma of the bladder was associated with the worst prognosis, whereas weak (P)RR positivity followed an intermediate course between intense and absent immunohistochemical staining (26). Nevertheless, our study showed that patients with (P)RR-negative adenocarcinoma had a higher risk of recurrence. In addition, patients with IASLC Grade 3 adenocarcinoma showed an association between (P)RR-negative expression and a higher risk of recurrence.

Table II. *Association of (pro)renin receptor [(P)RR] expression with clinicopathological features and nuclear β-catenin expression in squamous cell carcinoma.*

Variables	N	(P)RR expression				*p*-Value
		Negative	(%)	Positive	(%)	
Sex						0.887
Female	26	11	(42)	15	(58)	
Male	201	88	(44)	113	(56)	
Age						0.725
≤65	39	18	(46)	21	(54)	
>65	188	81	(43)	107	(57)	
Pathological stage						**0.012**
0	0	0	(0)	0	(0)	
I	130	50	(38)	80	(62)	
II	71	41	(58)	30	(42)	
III	26	8	(31)	18	(69)	
Histology						0.882
Keratinizing	152	68	(45)	84	(55)	
Non-keratinizing	60	25	(42)	35	(58)	
Basaloid	15	6	(40)	9	(60)	
STAS						0.396
Absent	142	65	(46)	77	(54)	
Present	85	34	(40)	51	(60)	
Lymphovascular invasion						0.586
Absent	94	43	(46)	51	(54)	
Present	133	56	(42)	77	(58)	
Nuclear β-catenin						**0.003**
Negative	163	81	(50)	82	(50)	
Positive	64	18	(28)	46	(72)	

STAS: Spread through air space. Significant *p*-values are shown in bold.

(P)RR is a receptor for renin and prorenin and consists of 350 amino acid, with a single transmembrane domain and a short cytoplasmic domain (1, 27). (P)RR is cleaved by proteolytic enzymes, such as furin, site-1 protease, and ADAM 19, in the trans-Golgi to generate a truncated form composed of the transmembrane and cytoplasmic domains and soluble (P)RR (27-30). Transmembrane and cytoplasmic domains copurify with V-ATPase. Soluble (P)RR is secreted, but its function remains unclear. (P)RR is an important component of the Wnt receptor complex that acts as an adaptor between LRP6 and V-ATPase (2). Upon Wnt stimulation, this signaling complex is endocytosed, generating a proton gradient across the vesicular membrane, which is essential for V-ATPase to phosphorylate LRP6 and thus activate β-catenin (2). Previous studies have suggested that (P)RR activity is promoted *via* the Wnt/β-catenin pathway in colorectal cancer, likely through the transmembrane and cytoplasmic domains of (P)RR. In this study, (P)RR immunoreactivity was observed in the cytoplasm of the tumor cells rather than the membrane, which may indicate increased levels of soluble (P)RR protein. This may have led to the contradictory results in previous reports.

Several studies have associated (P)RR expression with the tumorigenesis and progression of various cancers. Shibayama *et al*. suggested that (P)RR is involved in the development of pancreatic ductal adenocarcinoma and is dependent on Wnt/β-catenin signaling (14). Wang *et al*. demonstrated that (P)RR promoted human colorectal cancer through the Wnt/β-catenin signaling pathway and found that (P)RR levels in colorectal cancer were positively correlated with β-catenin translocation into the nucleus (12). In this study, (P)RR-positive and β-catenin-positive adenocarcinoma patients had a higher risk of recurrence and poorer prognosis. Previous studies have shown that the transmembrane and cytoplasmic domains of (P)RR may increase tumor malignancy *via* the Wnt/β-catenin pathway (12, 14). In our study, there was no relationship between (P)RR and β-catenin expression in adenocarcinomas, and we observed (P)RR immunoreactivity in the cytoplasm. Therefore, it remains unknown whether (P)RR activates the Wnt/β-catenin pathway among other factors activated in lung adenocarcinomas.

Study limitations. First, because it was based on immunohistochemistry using tissue microarrays, selection bias

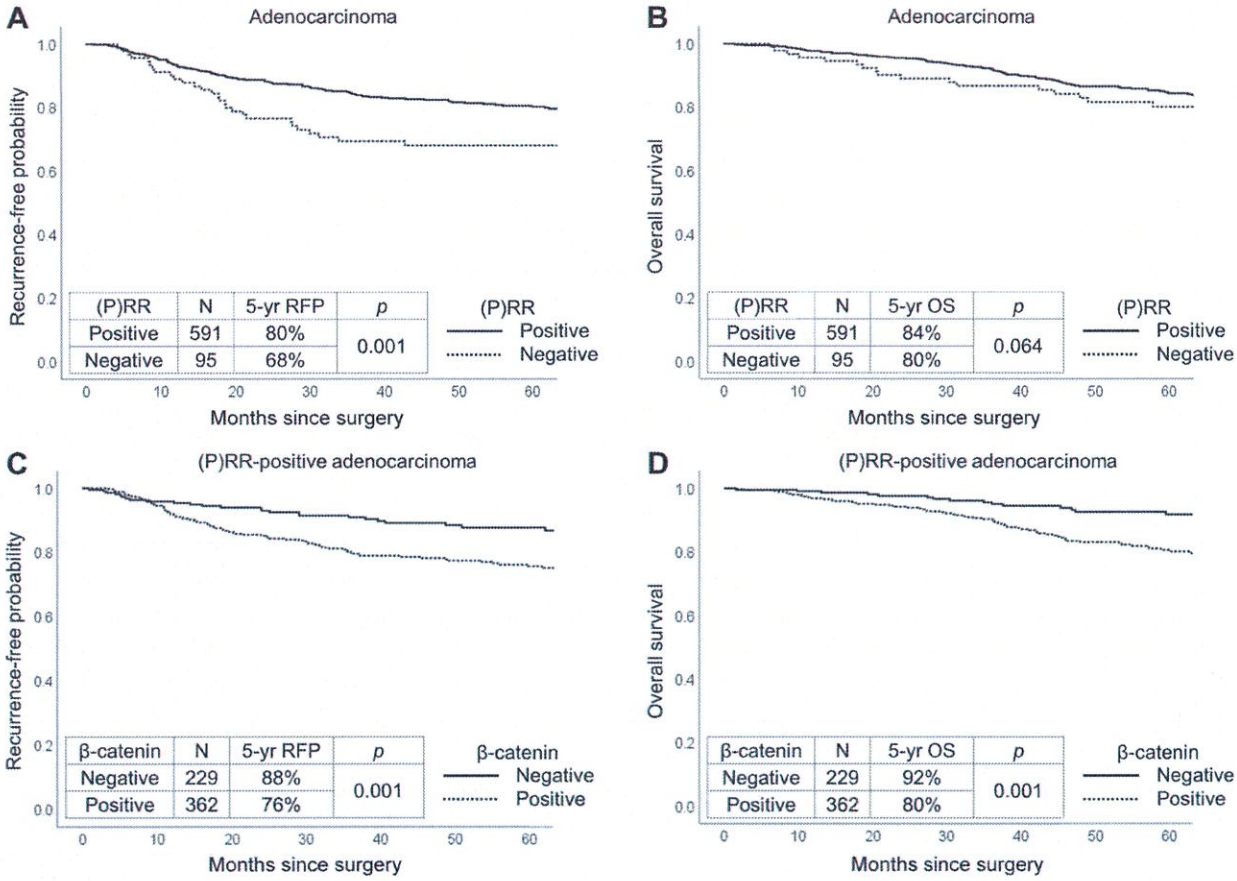

Figure 3. *(Pro)renin receptor [(P)RR] expression and patient outcomes [recurrence-free probability (RFP) and overall survival (OS)] in adenocarcinoma. The (A) RFP and (B) OS over 5 years for (P)RR-negative and -positive patients with adenocarcinoma. The (C) RFP and (D) OS over 5 years among (P)RR-positive patients that were β-catenin-positive or -negative.*

Table III. *Multivariate analysis of recurrence-free probability (RFP) in adenocarcinoma.*

Variable		HR	95%CI	*p*-Value
Pathological stage	0, I *vs.* II, III	0.41	0.28-0.59	**<0.001**
STAS	Present *vs.* absent	3.43	2.22-5.29	**<0.001**
Lymphovascular invasion	Present *vs.* absent	2.70	1.71-4.28	**<0.001**
(P)RR	Positive *vs.* negative	0.64	0.43-0.96	**0.031**
Nuclear β-catenin	Positive *vs.* negative	1.30	0.88-1.92	0.193

STAS: Spread through air space; (P)RR: (pro)renin receptor. Significant *p*-values are shown in bold.

was inevitable when selecting tumor sites for tissue microarray construction. To minimize selection bias, we used a relatively large tissue core (3 mm). Second, immunohistochemical analysis is not a suitable approach for investigating the roles of (P)RR and β-catenin; therefore, further experiments using cell lines and animal models are needed.

Conclusion

In this single-center study, (P)RR down-regulation was associated with a higher risk of recurrence in resected lung adenocarcinoma and high-grade subset adenocarcinoma. These results differ from other carcinomas, such as

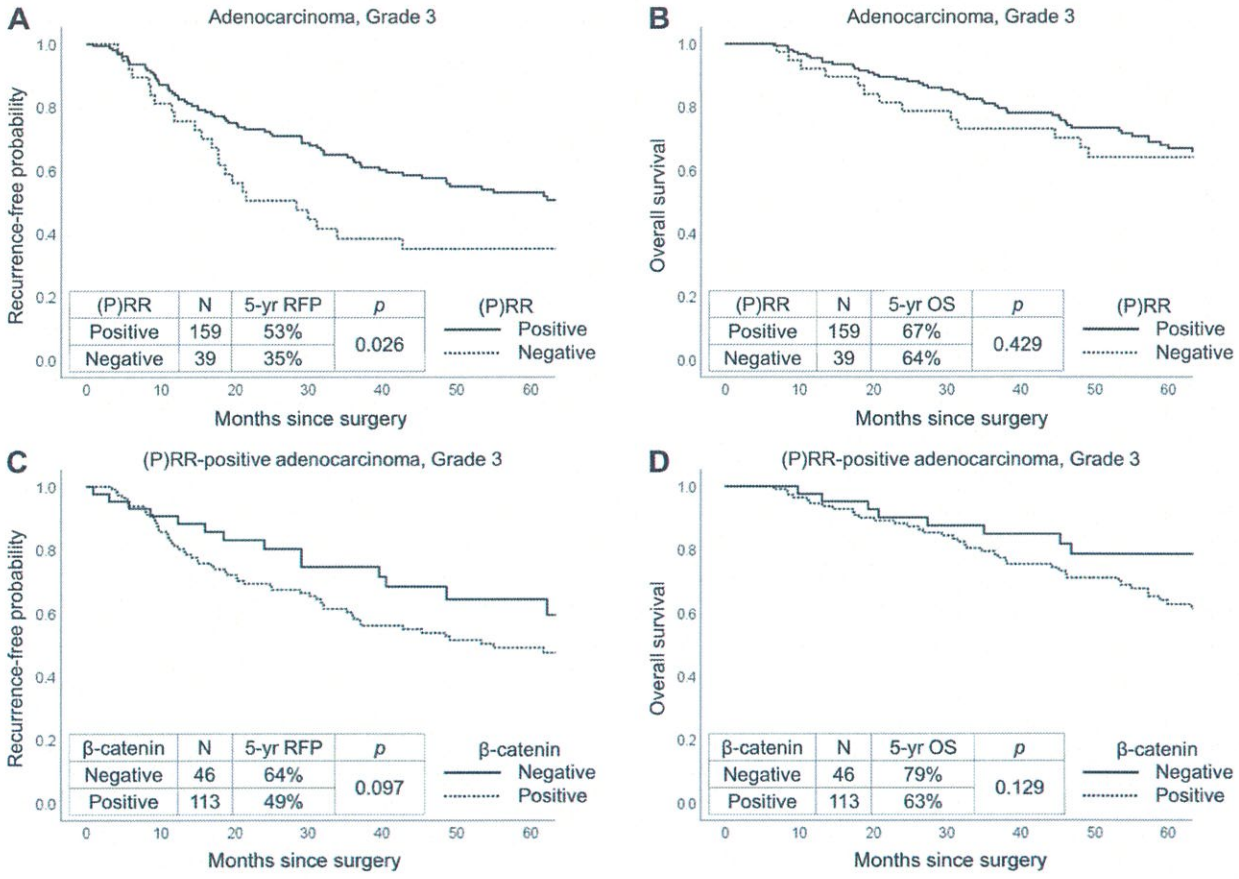

Figure 4. *(Pro)renin receptor [(P)RR] expression and patient outcomes [recurrence-free probability (RFP) and overall survival (OS)] in International Association for the Study of Lung Cancer Grade 3 adenocarcinoma. The (A) RFP and (B) OS over 5 years for (P)RR-negative and -positive patients with adenocarcinoma. The (C) RFP and (D) OS over 5 years among (P)RR-positive patients that were β-catenin-positive or -negative.*

colorectal cancer and invasive urothelial carcinoma. Therefore, caution should be exercised when using (P)RR as a therapeutic target for lung adenocarcinoma and other carcinomas.

Conflicts of Interest

The Authors have no conflicts of interest to declare in relation to this study.

Authors' Contributions

Nachino Kimura: Formal analysis, Investigation, Visualization, Writing–original draft. Kyuichi Kadota: Conceptualization, Funding acquisition, Methodology, Writing– review & editing. Emi Ibuki: Writing–review & editing. Ryou Ishikawa: Data curation. Toshihiro Ikeda: Resources. Chihiro Yoshida: Resources, Writing–review & editing. Toshiki Yajima: Supervision. Akira Nishiyama: Resources. Reiji Haba: Project administration.

Acknowledgements

The Authors would like to thank Editage (www.editage.jp) for English language editing.

Funding

This study did not receive any specific grants from funding agencies in the public, commercial, or non-profit sectors.

References

1 Nguyen G, Delarue F, Burcklé C, Bouzhir L, Giller T, Sraer JD: Pivotal role of the renin/prorenin receptor in angiotensin II production and cellular responses to renin. J Clin Invest 109(11): 1417-1427, 2002. DOI: 10.1172/JCI14276

2 Cruciat CM, Ohkawara B, Acebron SP, Karaulanov E, Reinhard C, Ingelfinger D, Boutros M, Niehrs C: Requirement of prorenin receptor and vacuolar H+-ATPase-mediated acidification for Wnt

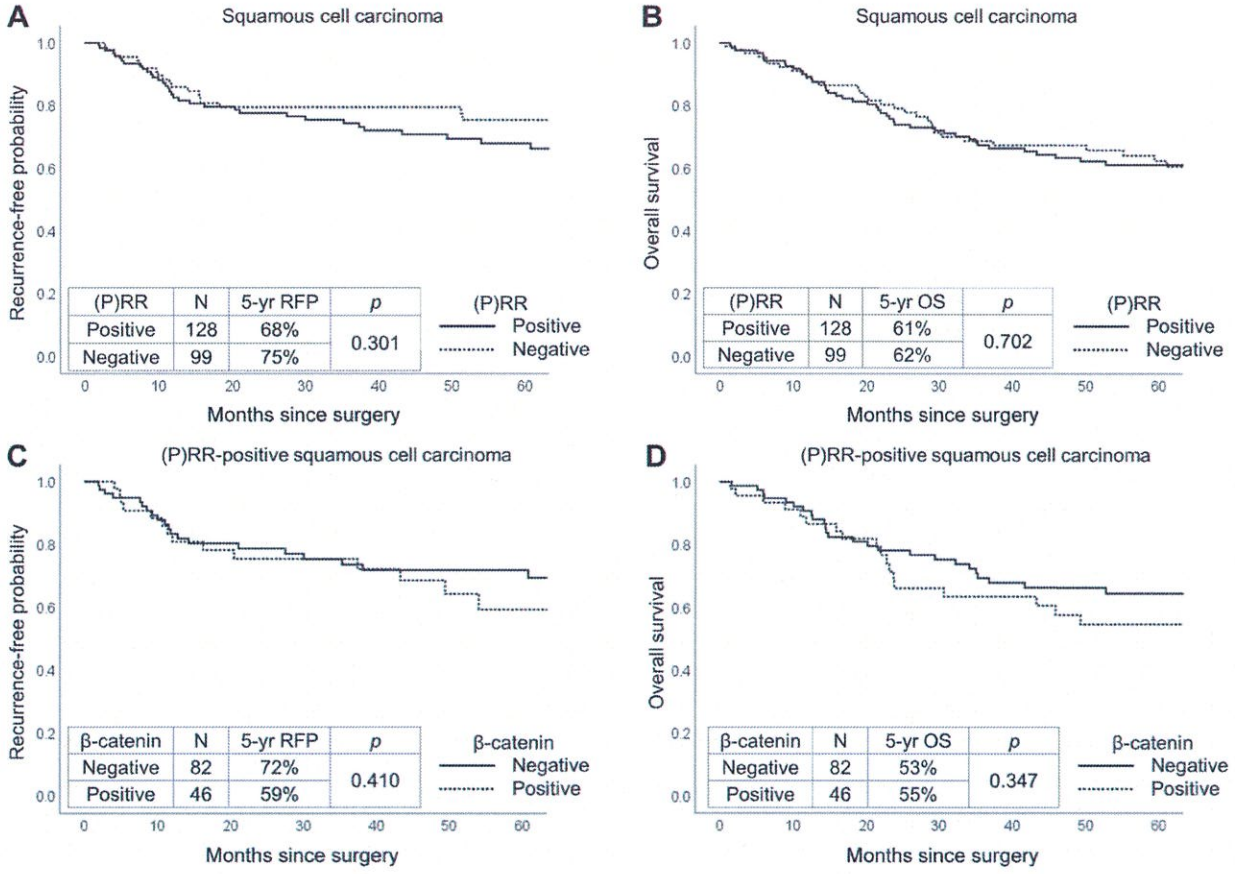

Figure 5. *(Pro)renin receptor [(P)RR] expression and patient outcomes (pro)renin receptor in squamous cell carcinoma. The (A) RFP and (B) OS over 5 years for (P)RR-negative and -positive patients with squamous cell carcinoma. The (C) RFP and (D) OS over 5 years among (P)RR-positive patients that were β-catenin-positive or -negative.*

signaling. Science 327(5964): 459-463, 2010. DOI: 10.1126/science.1179802

3 Bernhard SM, Seidel K, Schmitz J, Klare S, Kirsch S, Schrezenmeier E, Zaade D, Meyborg H, Goldin-Lang P, Stawowy P, Zollmann FS, Unger T, Funke-Kaiser H: The (pro)renin receptor ((P)RR) can act as a repressor of Wnt signalling. Biochem Pharmacol 84(12): 1643-1650, 2012. DOI: 10.1016/j.bcp.2012.09.020

4 Duchartre Y, Kim YM, Kahn M: The Wnt signaling pathway in cancer. Crit Rev Oncol Hematol 99: 141-149, 2016. DOI: 10.1016/j.critrevonc.2015.12.005

5 Huang Y, Wongamorntham S, Kasting J, McQuillan D, Owens RT, Yu L, Noble NA, Border W: Renin increases mesangial cell transforming growth factor-β1 and matrix proteins through receptor-mediated, angiotensin II-independent mechanisms. Kidney Int 69(1): 105-113, 2006. DOI: 10.1038/sj.ki.5000011

6 Kinouchi K, Ichihara A, Sano M, Sun-Wada GH, Wada Y, Ochi H, Fukuda T, Bokuda K, Kurosawa H, Yoshida N, Takeda S, Fukuda K, Itoh H: The role of individual domains and the significance of shedding of ATP6AP2/(pro)renin receptor in vacuolar H(+)-ATPase biogenesis. PLoS One 8(11): e78603, 2013. DOI: 10.1371/journal.pone.0078603

7 Burcklé C, Bader M: Prorenin and its ancient receptor. Hypertension 48(4): 549-551, 2006. DOI: 10.1161/01.HYP.0000241132.48495.df

8 Schroten NF, Gaillard CA, van Veldhuisen DJ, Szymanski MK, Hillege HL, de Boer RA: New roles for renin and prorenin in heart failure and cardiorenal crosstalk. Heart Fail Rev 17(2): 191-201, 2012. DOI: 10.1007/s10741-011-9262-2

9 Ichihara A, Sakoda M, Kurauchi-Mito A, Kaneshiro Y, Itoh H: Renin, prorenin and the kidney: a new chapter in an old saga. J Nephrol 22(3): 306-311, 2009.

10 Zhan T, Rindtorff N, Boutros M: Wnt signaling in cancer. Oncogene 36(11): 1461-1473, 2017. DOI: 10.1038/onc.2016.304

11 Peng H, Li W, Seth DM, Nair AR, Francis J, Feng Y: (Pro)renin receptor mediates both angiotensin II-dependent and -independent oxidative stress in neuronal cells. PLoS One 8(3): e58339, 2013. DOI: 10.1371/journal.pone.0058339

12 Wang J, Shibayama Y, Zhang A, Ohsaki H, Asano E, Suzuki Y, Kushida Y, Kobara H, Masaki T, Wang Z, Nishiyama A: (Pro)renin receptor promotes colorectal cancer through the

Wnt/beta-catenin signalling pathway despite constitutive pathway component mutations. Br J Cancer 120(2): 229-237, 2019. DOI: 10.1038/s41416-018-0350-0

13 Ohba K, Suzuki T, Nishiyama H, Kaneko K, Hirose T, Totsune K, Sasano H, Takahashi K: Expression of (pro)renin receptor in breast cancers and its effect on cancercell proliferation. Biomed Res 35(2): 117-126, 2014. DOI: 10.2220/biomedres.35.117

14 Shibayama Y, Fujimori T, Nguyen G, Hirose T, Totsune K, Ichihara A, Kitada K, Nakano D, Kobori H, Kohno M, Masaki T, Suzuki Y, Yachida S, Nishiyama A: (Pro)renin receptor is crucial for Wnt/β-catenin-dependent genesis of pancreatic ductal adenocarcinoma. Sci Rep 5: 8854, 2015. DOI: 10.1038/srep08854

15 Kouchi M, Shibayama Y, Ogawa D, Miyake K, Nishiyama A, Tamiya T: (Pro)renin receptor is crucial for glioma development *via* the Wnt/β-catenin signaling pathway. J Neurosurg 127(4): 819-828, 2017. DOI: 10.3171/2016.9.Jns16431

16 Yamamoto H, Kaneko K, Ohba K, Morimoto R, Hirose T, Satoh F, Totsune K, Takahashi K: Increased expression of (pro)renin receptor in aldosterone-producing adenomas. Peptides 49: 68-73, 2013. DOI: 10.1016/j.peptides.2013.08.022

17 de Sousa EMF, Vermeulen L, Richel D, Medema JP: Targeting Wnt signaling in colon cancer stem cells. Clin Cancer Res 17(4): 647-653, 2011. DOI: 10.1158/1078-0432.Ccr-10-1204

18 Kurayoshi M, Oue N, Yamamoto H, Kishida M, Inoue A, Asahara T, Yasui W, Kikuchi A: Expression of Wnt-5a is correlated with aggressiveness of gastric cancer by stimulating cell migration and invasion. Cancer Res 66(21): 10439-10448, 2006. DOI: 10.1158/0008-5472.Can-06-2359

19 Howe LR, Brown AM: Wnt signaling and breast cancer. Cancer Biol Ther 3(1): 36-41, 2004. DOI: 10.4161/cbt.3.1.561

20 El Wakil A, Lalli E: The Wnt/beta-catenin pathway in adrenocortical development and cancer. Mol Cell Endocrinol 332(1-2): 32-37, 2011. DOI: 10.1016/j.mce.2010.11.014

21 Liu J, Zhou Y, Liu Y, Li L, Chen Y, Liu Y, Feng Y, Yosypiv IV, Song R, Peng H: (Pro)renin receptor regulates lung development *via* the Wnt/β-catenin signaling pathway. Am J Physiol Lung Cell Mol Physiol 317(2): L202-L211, 2019. DOI: 10.1152/ajplung.00295.2018

22 Stewart DJ: Wnt signaling pathway in non-small cell lung cancer. J Natl Cancer Inst 106(1): djt356-djt356, 2014. DOI: 10.1093/jnci/djt356

23 Ishikawa R, Kadota K, Ikeda T, Yoshida C, Kimura N, Ibuki E, Go T, Yokomise H, Haba R: Prognostic impact of tumor-infiltrating lymphocytes and neutrophils in resected non-small cell lung carcinoma. Hum Pathol 125: 87-96, 2022. DOI: 10.1016/j.humpath.2022.04.012

24 Ikeda T, Kadota K, Yoshida C, Ishikawa R, Go T, Haba R, Yokomise H: The epithelial-mesenchymal transition phenotype is associated with the frequency of tumor spread through air spaces (STAS) and a high risk of recurrence after resection of lung carcinoma. Lung Cancer 153: 49-55, 2021. DOI: 10.1016/j.lungcan.2021.01.004

25 Fujimori T, Shibayama Y, Kanda T, Suzuki K, Ogawa D, Ishikawa R, Kadota K, Matsunaga T, Tamiya T, Nishiyama A, Miyake K: Effects of a monoclonal antibody against (pro)renin receptor on gliomagenesis. Sci Rep 13(1): 808, 2023. DOI: 10.1038/s41598-023-28133-x

26 Larrinaga G, Calvete-Candenas J, Solano-Iturri JD, Martín AM, Pueyo A, Nunes-Xavier CE, Pulido R, Dorado JF, López JI, Angulo JC: (Pro)renin receptor is a novel independent prognostic marker in invasive urothelial carcinoma of the bladder. Cancers (Basel) 13(22): 5642, 2021. DOI: 10.3390/cancers13225642

27 Nguyen G, Muller DN: The biology of the (pro)renin receptor. J Am Soc Nephrol 21(1): 18-23, 2010. DOI: 10.1681/asn.2009030300

28 Cousin C, Bracquart D, Contrepas A, Corvol P, Muller L, Nguyen G: Soluble form of the (pro)renin receptor generated by intracellular cleavage by furin is secreted in plasma. Hypertension 53(6): 1077-1082, 2009. DOI: 10.1161/hypertensionaha.108.127258

29 Nakagawa T, Suzuki-Nakagawa C, Watanabe A, Asami E, Matsumoto M, Nakano M, Ebihara A, Uddin MN, Suzuki F: Site-1 protease is required for the generation of soluble (pro)renin receptor. J Biochem 161(4): 369-379, 2017. DOI: 10.1093/jb/mvw080

30 Yoshikawa A, Aizaki Y, Kusano K, Kishi F, Susumu T, Iida S, Ishiura S, Nishimura S, Shichiri M, Senbonmatsu T: The (pro)renin receptor is cleaved by ADAM19 in the Golgi leading to its secretion into extracellular space. Hypertens Res 34(5): 599-605, 2011. DOI: 10.1038/hr.2010.284

Received October 5, 2023
Revised November 8, 2023
Accepted November 9, 2023