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Original Article

ORIGINAL ARTICLE

Influenza vaccination is associated with lower risk of renal cell carcinoma among chronic kidney disease patients: a population-based cohort study

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ABSTRACT

Background. Chronic kidney disease (CKD) patients possess a higher risk for renal cell carcinoma (RCC) possibly because of related underlying inflammation and immune dysregulation. In the current population-based cohort study, we evaluate the effects of influenza vaccination on RCC among CKD patients.

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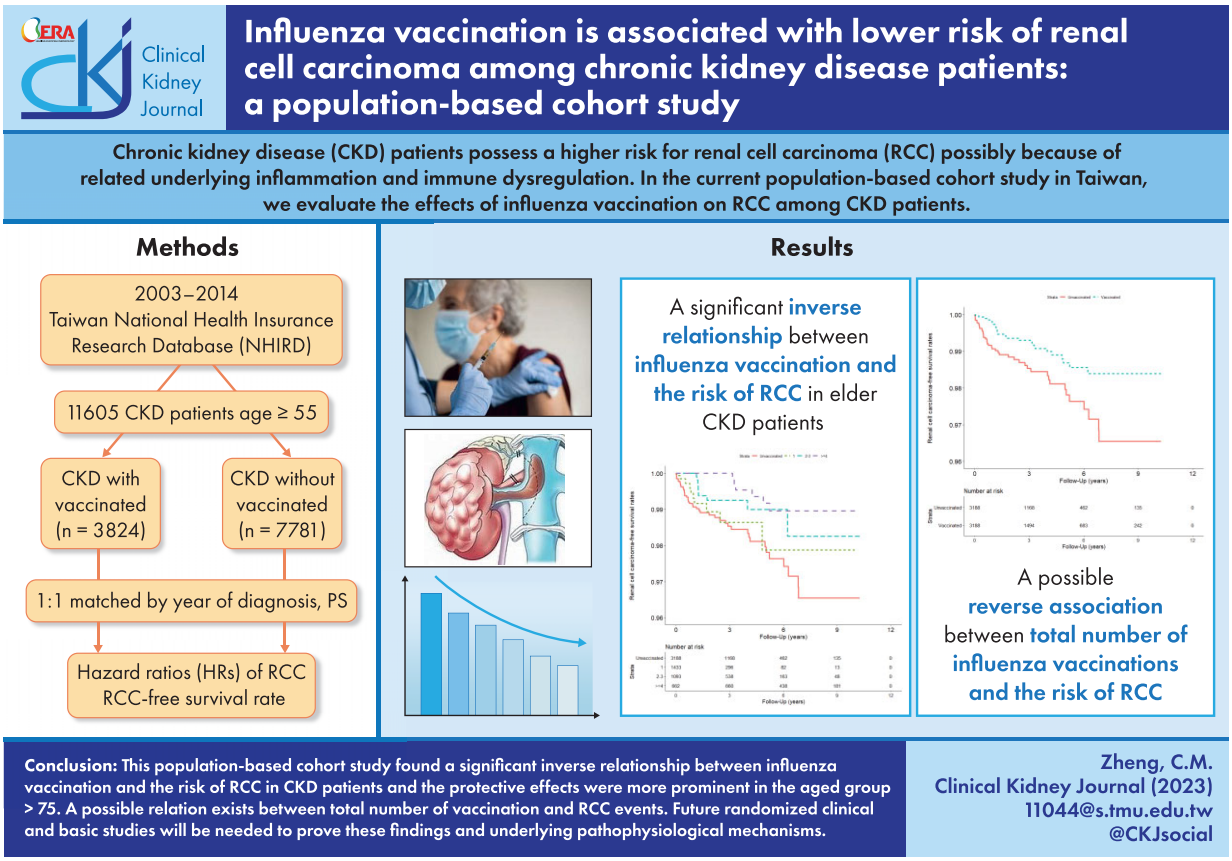
Methods. We analysed the vaccinated and unvaccinated CKD patients (≥55 years of age) identified from the Taiwan National Health Insurance Database. Propensity score matching was used to reduce the selection bias. Subgroup analyses based on comorbid conditions, dialysis status and vaccinated dosages were also conducted.
Results. The incidence of RCC decreased significantly in the vaccinated compared with unvaccinated group {unadjusted hazard ratio [HR] 0.50 [95% confidence interval (CI) 0.31–0.81], $P < .01$; adjusted HR 0.46 [95% CI 0.28–0.75], $P < .01$}. Such protective effects of influenza vaccination were noted significantly among those ≥75 years of age [unadjusted HR 0.29 (95% CI 0.12–0.74), $P < .01$; adjusted HR 0.22 (95% CI 0.08–0.58), $P < .01$]. A reverse association was noted between the total number of vaccinations and RCC events in both unadjusted and adjusted models. The Kaplan–Meier estimates of the RCC events showed significantly higher free survival rates in the vaccinated as compared with the unvaccinated patients (logrank $P = .005$).
Conclusion. This population-based cohort study found a significant inverse relationship between influenza vaccination and the risk of RCC in CKD patients and the protective effects were more prominent in patients >75 years of age. A possible relation exists between the total number of vaccinations and RCC events. Future randomized clinical and basic studies will be needed to prove these findings and underlying pathophysiological mechanisms.

GRAPHICAL ABSTRACT



Keywords: chronic inflammation, chronic kidney disease, immune dysfunction, influenza vaccination, renal cell carcinoma

INTRODUCTION

Chronic kidney disease (CKD) is a major global public health problem and Taiwan has a relatively high incidence and prevalence of CKD and end-stage kidney disease (ESKD) compared with other countries [1, 2]. Patients with CKD are at an increased risk of renal cell carcinoma (RCC) [3]. Huang *et al.* [4] demonstrated that 26% of RCC patients had underlying CKD. Consistent evidence of considerable risk for RCC and other malignancies was observed among ESKD and kidney transplant recipients [5–9]. In a recent population study, Lowrance *et al.* [10] reported a close relationship between decreased estimated glomerular infiltration rate (eGFR) and increased risk of RCC. Studies found that such excessive risk of cancer began as early as an eGFR of 55 ml/min/1.73 m^2 [11, 12] and linearly increased along with CKD deterioration. The underlying biologic mechanisms between CKD and RCC risk might be related to

uraemia-induced immune dysfunction [13]. In a recent study, Rosenzweig *et al*. [14] revealed the association between nephrectomy type and specified metabolites with post-nephrectomy CKD status in operated RCC patients. Furthermore, CKD and RCC share common aetiologic risk factors, including tobacco abuse, hypertension, diabetes mellitus and toxins [15–20].

CKD patients had a higher risk of influenza infection [21, 22], which increased the chance of hospitalisation and cardiovascular mortality [23, 24]. In relation to observational studies, influenza vaccination reduced the risk of cardiovascular events and related morbidity and mortality among CKD/ESKD patients [25, 26]. Although not many studies are available, it was shown in animal models that *Listeria monocytogenes* vaccine can reduce tumour growth through antigen T-cell–specific mechanisms [27, 28]. Newman *et al*. [29] reported that intratumoral immune injections introduce pathogens and related components that augment the systemic antitumour immunity.

The Taiwan health authority has recognized the risk of influenza infection in CKD patients and advised an annual government-funded influenza vaccination as recommended by the Advisory Committee on Immunization Practices (ACIP) [30]. Moreover, one study showed the potential immune mechanisms involved in influenza vaccination in the inhibition of the development of human cancers [29]. As there is little information on the potential benefit of influenza vaccination in reducing RCC events in CKD patients, we conducted a population-based cohort study to determine the risk of RCC among CKD patients receiving annual influenza vaccination.

MATERIALS AND METHODS

Data source

Taiwan's National Health Insurance (NHI) program, launched in 1995, covers 99% of the population of Taiwan; currently >23 million people. The NHI Research Database (NHIRD), which is maintained by the Health and Welfare Data Science Center, has been extensively analysed and validated [31–34]. All researchers using the NHIRD and its data subsets must sign an agreement declaring that they have no intention of obtaining information that could potentially violate the privacy of patients or care providers. The current study protocol was approved by the NHIRD research committee and the Taipei Medical University Joint Institutional Review Board (N201804043).

Study cohort and study design

The patients enrolled in the present study were recorded as having CKD between 1 January 2003 and 31 December 2014, with all diagnoses corresponding to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code 585.X. According to Taiwan's national health policy, patients ≥55 years of age with chronic diseases are recommended to receive mandatory influenza vaccination yearly without extra fees. Thus we chose those ≥55 years of age to avoid unnecessary bias. Patients ≥55 years of age ($N = 11\,605$) with an ICD-9-CM 585.X diagnosis code were grouped as CKD only if the diagnosis code appeared at least twice during outpatient visits or once in an inpatient visit. All stages of CKD were recruited, including those undergoing renal replacement therapy. Patients with renal transplantation, subjects with any inpatient or outpatient diagnosis related to any cancers before the date of cohort enter and subjects who had influenza vaccination within 1 year before the date of cohort entry were excluded (Fig. 1). Vaccination status was identified by code V048 and/or the use of vaccine (confirmed by drug codes). After 1:1 propensity score matching and in the same year of CKD diagnosis, the patients were divided into vaccinated ($n = 3188$) and unvaccinated ($n = 3188$) groups (Fig. 1). To avoid immortal time bias [35], the vaccination date of the patients in the vaccinated group was defined as the index or cohort entry date. In the matched pairs, the participants who received and did not receive vaccination were assigned the same index date (i.e. the vaccination date) for follow-up. The study endpoint was the initial diagnosis of RCC (ICD-9-CM code 189.X). All patients were followed until RCC diagnosis, withdrawal from NHI, loss to follow-up, death or 31 December 2014. Except for those patients diagnosed as having RCC, the other data were censored.

Potential confounders

The potential confounders of this cohort included sociodemographic characteristics (age, sex, urbanization level and monthly income), comorbidities [coronary artery disease (CAD), heart failure (HF), peripheral vascular disease, cerebral vascular accident, dementia, pulmonary disease, connective tissue disease, peptic ulcer, chronic liver disease, hypertension, diabetes, hyperlipidaemia, central/peripheral nervous system damage, depression], medication use [acetylsalicylic acid, statins, renin–angiotensin–aldosterone system inhibitors (RAASis) and metformin] and CKD severity (CKD-related inpatient and outpatient visits, dialysis).

Matching factors

Propensity score matching, which involves assigning levels of 0 or 1 to a treatment variable, given a set of known variables, was used to adjust for potential selection bias, confounders and differences between treatment groups in observational studies [36]. In the present study, the propensity score of each vaccinated patient was estimated by logistic regression, with the following potential confounders associated with vaccine introduction: sociodemographic characteristics (age, sex, urbanization level and monthly income), comorbidities (CAD, HF, peripheral vascular disease, cerebral vascular accident, dementia, pulmonary disease, connective tissue disease, peptic ulcer, chronic liver disease, hypertension, diabetes, hyperlipidaemia, central/peripheral nervous system damage, depression), medication use (acetylsalicylic acid, statins, RAASis and metformin) and CKD severity (CKD-related inpatient and outpatient visits, dialysis). The vaccinated and unvaccinated patients were then matched using the propensity scores and a 1:1 nearest-neighbour algorithm. As previously suggested [37], the calliper width was set as 0.03 of the pooled standard deviation of the logit of the propensity scores. Finally, the patients were divided into vaccinated ($n = 3188$) and unvaccinated ($n = 3188$) groups.

Statistical analysis

In the present study, the categorical data are expressed as numbers and percentages, while the quantitative data are presented as mean ± standard deviation (SD). The balance of characteristics was assessed by estimating the standardized differences (StDiffs) between the vaccinated and unvaccinated groups. Empirically, an absolute value of StDiffs >0.1 (10%) represents a meaningful imbalance in a given variable between two groups. A Cox proportional hazards model was used to calculate the hazard ratios (HRs) to determine the differences in the risk of RCC

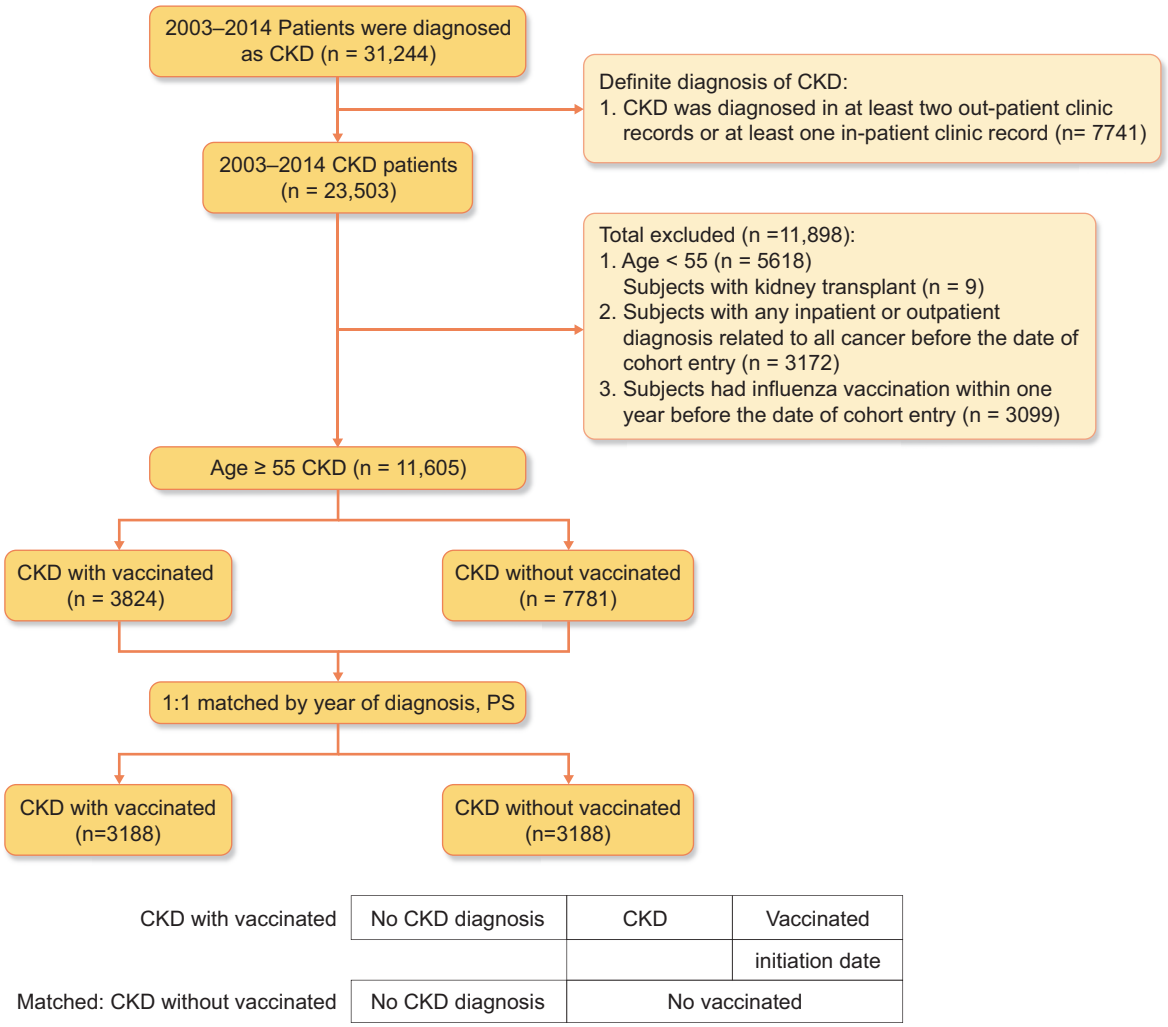


Figure 1: Data selection process.

between the groups. The adjusted HRs were HRs that were adjusted according to the confounders. Sensitivity analysis can improve the understanding of the effects of demographic data including frequency of vaccination and comorbidity in epidemiologic database studies [38]. Thus, in the present sensitivity analysis, the patients were stratified to estimate the impact of age, sex, dialysis status, CKD-related inpatient visits, CAD, HF, peripheral vascular disease, cerebral vascular accident, peptic ulcer, chronic liver disease, hypertension, diabetes and hyperlipidaemia on the incidence of RCC with or without vaccination. The RCC-free survival rate in the vaccinated and unvaccinated patients with CKD was calculated using the Kaplan–Meier method. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA). A two-tailed *P*-value <.05 was considered significant.

RESULTS

A total of 31 244 patients were diagnosed with CKD according to the 2003–2014 NHI database and 7741 CKD patients had a definite diagnosis of CKD according to our definition (Fig. 1). After the exclusion of patients <55 years of age ($n = 5618$), kidney transplant patients ($n = 9$), inpatient and outpatient diagnoses with any cancer ($n = 3172$) and those who received vaccination within 1 year before the date of cohort entry ($n = 3099$), 11 605 patients with CKD were included in this study (Fig. 1). A total of 3824 CKD patients received influenza vaccination and 7781 CKD patients did not receive influenza vaccination (Fig. 1). After 1:1 propensity score matching and in the same year of CKD diagnosis, the patients were divided into vaccinated ($n = 3188$) and unvaccinated ($n = 3188$) groups (Fig. 1). Table 1 shows the baseline characteristics balance before and after propensity score matching by year of diagnosis. Table 2 presents the results of propensity score matching adjusted for potential confounders defined in the method.

The incidence of RCC was reduced significantly in the vaccinated group compared with the unvaccinated group [unadjusted HR 0.50 (95% CI 0.31–0.81), $P < .01$; adjusted HR 0.46 (95% CI, 0.28–0.75), $P < .01$]. The protective effects of the influenza vaccination were significant among those ≥75 years of age [unadjusted HR 0.29 (95% CI 0.12–0.74), $P < .01$; adjusted HR 0.22 (95% CI 0.08–0.58), $P < .01$], but not among those ages 55–74 years [unadjusted HR 0.65 (95% CI 0.36–1.16), $P > .05$; adjusted HR 0.59 (95% CI 0.32–1.09), $P > .05$]. Furthermore, the HR of RCC in the vaccinated group significantly decreased in both sexes after adjustments for modifiable risk factors, with a lower risk in females compared with males [adjusted HR 0.39 (95% CI 0.19–0.78), $P < .01$ in females; adjusted HR 0.41 (95% CI 0.19–0.85), $P < .05$ in males].

Table 1: Pooled baseline characteristics balance before and after propensity score matching.

	Before matching					After matching				
	CKD without vaccination ($n = 7781$)		CKD with vaccination ($n = 3824$)		Standardized difference	CKD without vaccination ($n = 3188$)		CKD with vaccination ($n = 3188$)		Standardized difference
Characteristics	*n*	%	*n*	%		*n*	%	*n*	%	
Propensity score, mean ± SD	0.30 ± 0.14		0.39 ± 0.14		0.686	0.37 ± 0.14		0.38 ± 0.14		0.021
CKD-related inpatient visits, *n*										
0	5566	71.53	2592	67.78	−0.082	2160	67.75	2188	68.63	0.019
1	1260	16.19	549	14.36	−0.051	465	14.59	455	14.27	−0.009
≥2	955	12.27	683	17.86	0.157	563	17.66	545	17.10	−0.015
Dialysis	1807	23.22	1046	27.35	0.095	879	27.57	867	27.20	−0.008
Age (years), mean ± SD	70.28 ± 10.38		72.28 ± 8.15		0.214	72.01 ± 8.82		72.28 ± 8.43		0.031
55–64	2982	38.32	836	21.86	−0.365	779	24.44	748	23.46	−0.023
65–74	2182	28.04	1581	41.34	0.282	1206	37.83	1230	38.58	0.015
≥75	2617	33.63	1407	36.79	0.066	1203	37.74	1210	37.95	0.005
Sex										
Female	3432	44.11	1677	43.85	−0.005	1391	43.63	1405	44.07	0.009
Male	4349	55.89	2147	56.15	0.005	1797	56.37	1783	55.93	−0.009
Comorbidities										
CAD	3764	48.37	1895	49.56	0.024	1588	49.81	1649	51.73	0.038
HF	1877	24.12	799	20.89	−0.077	688	21.58	721	22.62	0.025
Peripheral vascular disease	1411	18.13	604	15.79	−0.062	503	15.78	530	16.62	0.023
Cerebral vascular accident	2774	35.65	1293	33.81	−0.039	1087	34.10	1142	35.82	0.036
Dementia	628	8.07	272	7.11	−0.036	244	7.65	249	7.81	0.006
Pulmonary disease	3889	49.98	1882	49.22	−0.015	1526	47.87	1645	51.60	0.075
Connective tissue disease disorder	526	6.76	231	6.04	−0.029	204	6.40	210	6.59	0.008
Peptic ulcer	4060	52.18	1879	49.14	−0.061	1559	48.90	1625	50.97	0.041
Chronic liver disease	2719	34.94	1188	31.07	−0.083	979	30.71	1032	32.37	0.036
Hypertension	6430	82.64	3117	81.51	−0.029	2520	79.05	2580	80.93	0.047
Diabetes	4349	55.89	1882	49.22	−0.134	1607	50.41	1634	51.25	0.017
Hyperlipidaemia	4373	56.20	1897	49.61	−0.132	1486	46.61	1552	48.68	0.041
Paraplegia	404	5.19	155	4.05	−0.054	135	4.23	141	4.42	0.009
Depression	453	5.82	186	4.86	−0.043	157	4.92	171	5.36	0.020
Medication use										
Acetylsalicylic acid	3004	38.61	2260	59.10	0.419	1777	55.74	1800	56.46	0.015
Statin	2783	35.77	1630	42.63	0.141	1291	40.50	1342	42.10	0.032
RAASi	4811	61.83	2949	77.12	0.337	2364	74.15	2410	75.60	0.033
Metformin	1603	20.60	980	25.63	0.119	783	24.56	802	25.16	0.014
Level of urbanization										
Urban	5600	71.97	2457	64.25	−0.166	2124	66.62	2085	65.40	−0.026
Suburban	1507	19.37	875	22.88	0.086	705	22.11	711	22.30	0.005
Rural	674	8.66	492	12.87	0.136	359	11.26	392	12.30	0.032
Monthly income (NT$)										
0	910	11.70	496	12.97	0.039	421	13.21	391	12.26	−0.028
1–33 300	4807	61.78	2740	71.65	0.211	2214	69.45	2246	70.45	0.022
≥33 301	2064	26.53	588	15.38	−0.277	553	17.35	551	17.28	−0.002

Standardized difference: difference in the mean or proportions divided by the standard error; imbalance between groups was defined as absolute value >0.10 (corresponding to a small effect size).

Propensity score matched is adjusted for CKD-related inpatient visits, dialysis, age, sex, CAD, HF, peripheral vascular disease, cerebral vascular accident, dementia, pulmonary disease, connective tissue disorder, peptic ulcer, chronic liver disease, hypertension, diabetes, hyperlipidaemia, paraplegia, depression, acetylsalicylic acid, statin, RAASi, metformin, level of urbanization and monthly income.

Table 2: Risk of RCC among unvaccinated and vaccinated groups in the study cohort.

Groups ($N = 6376$)	CKD without vaccination (total follow-up 8598.58 person-years) Patients with RCC, n	Incidence rate (per 10^5 person-years) (95% CI)	CKD with Vaccinated (Total follow-up 10760.33 person-years) Patients with RCC, n	Incidence rate (per 10^5 person-years) (95% CI)	Unadjusted HR (95% CI)	Adjusted HR[e] (95% CI)
Whole cohort	43	500.1 (350.6–649.6)	26	241.6 (148.7–334.5)	0.50 (0.31–0.81)**	0.46 (0.28–0.75)**
Age, 55–74[a]	26	436.5 (268.7–604.3)	20	269.4 (151.4–387.5)	0.65 (0.36–1.16)	0.59 (0.32–1.09)
Age, ≥75[b]	17	643.3 (337.5–949.1)	6	179.8 (35.9–323.6)	0.29 (0.12–0.74)**	0.22 (0.08–0.58)**
Female[c]	24	663.6 (398.1–929.1)	14	296.0 (140.9–451.0)	0.47 (0.24–0.92)*	0.39 (0.19–0.78)**
Male[d]	19	381.4 (209.9–552.8)	12	199.0 (86.4–311.6)	0.54 (0.26–1.10)	0.41 (0.19–0.85)*

[a]Total follow-up 5956.02 person-years for CKD without vaccination and 7422.86 for CKD with vaccination.
[b]Total follow-up 2642.56 person-years for CKD without vaccination and 3337.47 for CKD with vaccination.
[c]Total follow-up 3616.48 person-years for CKD without vaccination and 4730.20 for CKD with vaccination.
[d]Total follow-up 4982.10 person-years for CKD without vaccination and 6030.13 for CKD with vaccination.
[e]Main model is adjusted for CKD-related inpatient visits, dialysis, age, sex, CAD, HF, peripheral vascular disease, cerebral vascular accident, dementia, pulmonary disease, connective tissue disorder, peptic ulcer, chronic liver disease, hypertension, diabetes, hyperlipidaemia, paraplegia, depression, acetylsalicylic acid, statin, RAASi, metformin, level of urbanization, monthly income.

Table 3 summarizes the risks of RCC according to the total number of vaccinations in different subgroups. Both unadjusted and adjusted risk reduction of RCC was noted in those with a higher total number of vaccinations. In subgroup analysis, a significant reduction of RCC was noted among those ≥75 years of age in both sexes with influenza vaccination, regardless of dialysis status and other comorbid conditions. The Kaplan–Meier estimates of the RCC events are shown in Fig. 2. The RCC event-free survival rates in the vaccinated group were significantly higher than in the unvaccinated group (logrank $P = .005$). The RCC event-free survival rates increased significantly in those with a higher total number of vaccinations (Fig. 3).

DISCUSSION

Our study demonstrated that CKD patients who had received influenza vaccination exhibited a lower risk of RCC events than those who were unvaccinated in both sexes and the protective effects were more prominent in patients ≥75 years of age. Among the dialysis patients, the risk of RCC events was lower in the vaccinated than the unvaccinated group. The cumulative RCC event-free survival rates in the vaccinated group were significantly higher than in the unvaccinated group. RCC event-free survival rates were positively related to the number of vaccinations. From the public health viewpoint, these findings are critical and no previous study revealed this relation.

Several biologic mechanisms have been proposed to explain the association between kidney function impairment and RCC. In brief, kidney dysfunction results in a state of chronic inflammatory and oxidative stress [39, 40] that provides a microenvironment favouring cancer development [41]. Furthermore, severe CKD creates a relative immunodeficiency status [42] that promotes cancer development. Studies have examined if certain medications for CKD patients (e.g. statins, antihypertensive agents) [43–48] increase cancer risk but found no evidence of their roles in RCC after adjustments for differential longitudinal use of medicines [10]. Several carcinogen-related microorganisms, including human papillomavirus (HPV), hepatitis B and C viruses and *Helicobacter pylori*, are well known to be associated with cancers. Viral and bacterial infections contracted by CKD patients, such as influenza, pneumonia, pharyngitis and sinusitis, could also create an inflammation and tumourigenic microenvironment [49–51]. Such infections potentially suppress and deteriorate the host immunity, favouring cancer development [51–54]. Cancer is further evolved and confounded by various carcinogen exposures, including smoking and air pollution [55, 56]. In contrast, cancer and precancerous states are related with inhibition of the immune system [49, 52, 57], with these patients at risk of contracting infections. Thus the mutual influence between infections and cancers regarding chronic inflammation and immunity before cancer development is an interesting issue to be investigated.

Infection is an important cause of non-cardiovascular morbidity and mortality among CKD patients [58]. Therefore, the Centers for Disease Control and Prevention Advisory Committee on Immunization Practices and the Kidney Disease: Improving Global Outcomes guidelines recommend annual seasonal influenza vaccines for CKD patients (Grade 1A) [59, 60]. Indeed, influenza vaccination has been shown to reduce the risk for pneumonia-/influenza-related hospitalizations and mortality [61–63]. Our previous study also revealed a reduction in the risk of lung cancer with influenza vaccination among diabetic patients [64]. Another study indicated that the frequency and severity of influenza infections were positively related to the risk of lung cancer events [65], however, the relation between many other solid cancers and influenza events is still unclear.

Aging, smoking and dialysis therapies increase the risk of RCC in CKD patients [66]. From our study, we found a possible relation between influenza vaccination and RCC risk in elderly CKD patients. We also found possible protective effects of influenza vaccination in patients ≥55 years of age in both sexes, which was significant in patients ≥75 years of age [65]. Since the underlying immunologic dysfunction of CKD is related with RCC risk [13] [67], the influenza vaccination–induced immunomodulation might explain its possible protective effects. Dialysis patients had a several-fold increase in the prevalence of RCC, regardless of the underlying cause [68–70]. We found that dialysis patients with influenza vaccination had a lower risk of RCC than those who were unvaccinated. The effects of influenza vaccination on dialysis patients still need to be studied.

Any innate immunity disruption through chemocarcinogen exposure in precancerous states, including chronic inflammation, smoking, environmental pollution or genetic conditions, might predispose to cancers [52, 53, 55]. Our data lack information on such chemocarcinogen exposure such as air pollution and smoking, genetics or lifestyles, and other comorbidities. As an observational study, we also had no available data on other possible precancerous indicators related with

Table 3: Subgroup analysis of vaccination in risk reduction of RCC.

		Vaccinated			
	Unvaccinated, adjusted HR (95% CI)	1 Adjusted HR (95% CI)	2–3 Adjusted HR (95% CI)	≥ 4 Adjusted HR (95% CI)	*P* for trend
Unadjusted	1.00	0.78 (0.39–1.56)	0.48 (0.23–0.98)*	0.34 (0.15–0.77)**	0.002
Model 1[a]	1.00	0.81 (0.40–1.62)	0.44 (0.21–0.91)*	0.35 (0.15–0.80)*	0.002
Main model[b]	1.00	0.74 (0.37–1.49)	0.37(0.18–0.78)**	0.36 (0.16–0.82)*	0.001
Subgroup effects					
Age (years)					
55–74	1.00	0.96 (0.42–2.19)	0.45 (0.18–1.13)	0.48 (0.19–1.23)	0.046
≥75	1.00	0.22 (0.05–1.05)	0.27 (0.08–0.94)*	0.14 (0.02–1.10)	0.006
Sex					
Female	1.00	0.67 (0.24–1.86)	0.27 (0.10–0.75)*	0.37 (0.12–1.17)	0.007
Male	1.00	0.74 (0.26–2.08)	0.30 (0.10–0.92)*	0.30 (0.09–1.07)	0.011
Dialysis					
No	1.00	0.41 (0.12–1.42)	0.41 (0.14–1.21)	0.23 (0.05–1.03)	0.014
Yes	1.00	1.00 (0.41–2.45)	0.31 (0.11–0.88)*	0.38 (0.14–1.08)	0.014
CKD-related outpatient visits					
0	1.00	0.27 (0.06–1.16)	0.25 (0.07–0.86)*	0.20 (0.04–0.86)*	0.003
1	1.00	0.22 (0.01–6.66)	0.58 (0.06–5.56)	1.17 (0.05–28.78)	0.918
≥2	1.00	1.86 (0.71–4.90)	0.36 (0.11–1.51)	0.46 (0.12–1.79)	0.085
CAD					
No	1.00	0.87 (0.35–2.16)	0.28 (0.10–0.82)*	0.41 (0.15–1.09)	0.011
Yes	1.00	0.57 (0.17–1.91)	0.56 (0.19–1.65)	0.26 (0.05–1.39)	0.071
HF					
No	1.00	0.82 (0.37–1.81)	0.39 (0.17–0.92)*	0.44 (0.18–1.09)	0.014
Yes	1.00	0.28 (0.04–1.84)	0.06 (0.01–0.35)**	–	0.002
Peripheral vascular disease					
No	1.00	0.77 (0.37–1.60)	0.32 (0.14–0.73)**	0.35 (0.15–0.85)*	0.001
Yes	1.00	0.33 (0.01–10.72)	0.24 (0.01–9.86)	0.93 (0.02–39.50)	0.697
Cerebral vascular accident					
No	1.00	0.93 (0.40–2.15)	0.45 (0.19–1.04)	0.49 (0.21–1.17)	0.032
Yes	1.00	0.38 (0.09–1.60)	0.12 (0.02–0.59)**	–	0.006
Pulmonary disease					
No	1.00	0.51 (0.17–1.49)	0.50 (0.20–1.25)	0.35 (0.12–1.03)	0.023
Yes	1.00	0.82 (0.30–2.22)	0.19 (0.05–0.71)*	0.37 (0.10–1.42)	0.014
Peptic ulcer					
No	1.00	0.95 (0.40–2.25)	0.39 (0.14–1.08)	0.29 (0.09–1.01)	0.015
Yes	1.00	0.44 (0.12–1.55)	0.33 (0.11–1.03)	0.45 (0.14–1.43)	0.045
Chronic liver disease					
No	1.00	0.48 (0.18–1.28)	0.29 (0.11–0.78)*	0.25 (0.09–0.75)*	0.001
Yes	1.00	1.22 (0.40–3.67)	0.65 (0.20–2.07)	0.54 (0.14–2.11)	0.306
Hypertension					
No	1.00	0.40 (0.06–2.65)	6.62 (0.92–47.77)	–	0.024
Yes	1.00	0.77 (0.34–1.71)	0.45 (0.20–1.00)*	0.47 (0.20–1.13)	0.023
Diabetes					
No	1.00	0.57 (0.20–1.64)	0.23 (0.07–0.78)*	0.43 (0.16–1.20)	0.011
Yes	1.00	1.02 (0.37–2.81)	0.71 (0.26–1.96)	0.28 (0.06–1.33)	0.115
Hyperlipidaemia					
No	1.00	0.49 (0.16–1.48)	0.32 (0.09–1.06)	0.33 (0.10–1.13)	0.015
Yes	1.00	0.81 (0.30–2.21)	0.46 (0.17–1.25)	0.34 (0.09–1.25)	0.047

*$P < .05$, **$P < .01$, ***$P < .001$.

[a]Model 1 is adjusted for CKD-related inpatient visits, dialysis, age, sex, CAD, HF, peripheral vascular disease, cerebral vascular accident, dementia, pulmonary disease, connective tissue disorder, peptic ulcer, chronic liver disease, hypertension, diabetes, hyperlipidaemia, paraplegia, depression, level of urbanization and monthly income.

[b]Main model is adjusted for CKD-related inpatient visits, dialysis, age, sex, CAD, HF, peripheral vascular disease, cerebral vascular accident, dementia, pulmonary disease, connective tissue disorder, peptic ulcer, chronic liver disease, hypertension, diabetes, hyperlipidaemia, paraplegia, depression, acetylsalicylic acid, statin, RAASi, metformin, level of urbanization and monthly income.

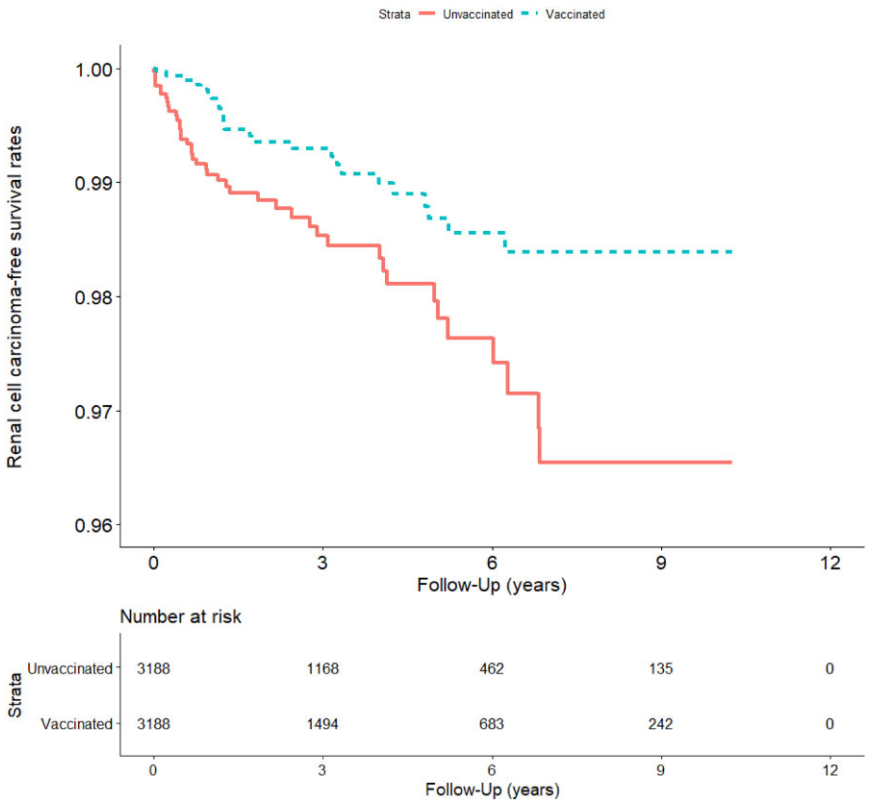


Figure 2: RCC events-free survival rates ($n = 6376$) from 1 January 2003 to 31 December 2014 in Taiwan, stratified by vaccinated and unvaccinated CKD patients (logrank test, $\chi^2 = 7.957$, df = 1, $P = .005$).

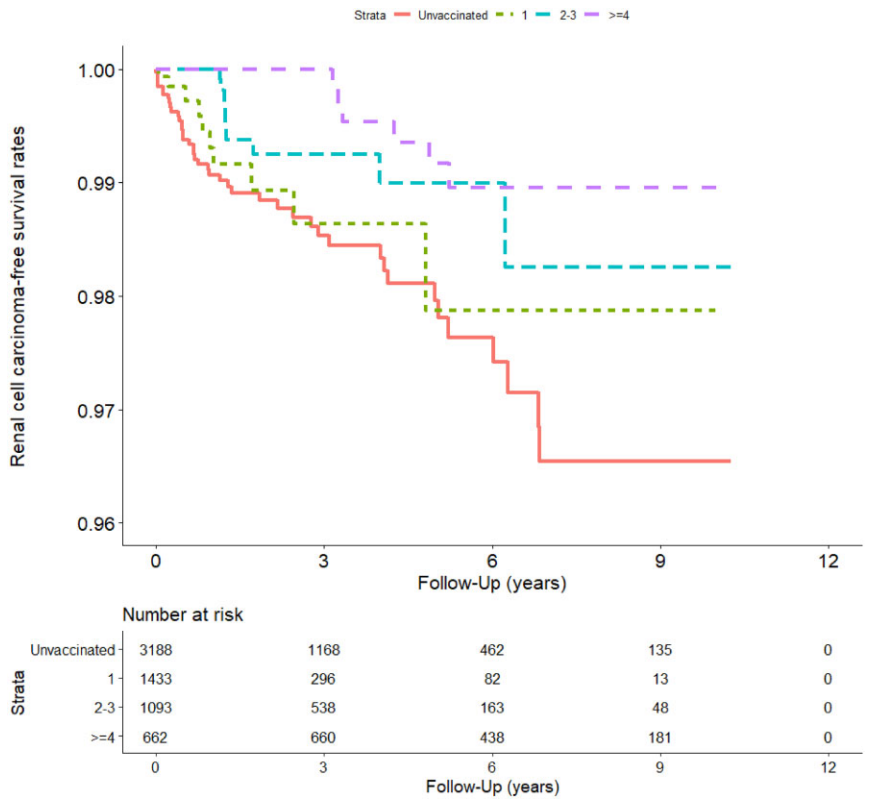


Figure 3: RCC events-free survival rates ($n = 6376$) from 1 January 2003 to 31 December 2014 in Taiwan, stratified according to the total number of vaccinations (logrank test, $\chi^2 = 10.013$, df = 3, $P = .018$).

oncogenesis, as monitored by immunity-related cells such as T-helper cells and B cells [71–73]. In this precancer period, possible aging and cumulative infection events increased the immune suppression and cancer promotion [49, 74]. This might explain our finding of a potential association between the total number of vaccinations and RCC-free survival years. Moreover, individuals who were vaccinated often had more contact with the healthcare system and might otherwise be in better health (e.g. tobacco, better control of comorbidities etc.).

Our study had several notable strengths. First, the total number of patients analysed in our study represents the largest sample size in published cohort studies examining RCC risk in CKD patients. Our study focused on CKD patients and excluded individuals being transplanted. Second, we decreased potential selection bias by using propensity score matching [35] and adjusted the statistical analyses for potential confounders. Third, the results of subgroup analyses of the protective effects of the influenza vaccination remained consistent.

This study also had several limitations. CKD and RCC diagnoses were ICD-9-CM based, which might be affected by diagnostic accuracy. However, Taiwan has launched nationwide CKD program, and all of ICD coding is uniformly used countrywide. This concern was mitigated by enrolling patients with at least two outpatient clinic records or at least one inpatient clinic record. Taiwan NHIRD data did not provide detailed lifestyle or RCC risk information, such as smoking, environmental exposures, occupation, nutrition, functional status and family history of cancers including RCC.

CONCLUSION

The current study showed that influenza vaccinations associated with a lower risk of RCC in elderly CKD, including dialysis, patients. We recommend annual influenza vaccinations in elderly CKD patients regardless of sex and comorbid conditions, and additional or booster influenza vaccinations might be considered. Whether the RCC preventive effects result from decreased influenza/pneumonia events or come directly from the influenza vaccine remain unclear. Future clinical studies are warranted to examine the causal relationship of the influenza vaccine and RCC in CKD patients, as well as molecular studies to investigate the underlying mechanisms of the vaccine.

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AUTHORS' CONTRIBUTIONS

Conceptualization, L.-C.W. and W.-C.C.; Methodology, Z.-J.Q. and F.-Y.A.; Software, T.-K.Y. and K.-W.T.; Validation, L.-H.T., L.-J.C. and H.-Y.H.; Formal Analysis, L.-Y.F., L.K.C. and D.-S.W.; Investigation, C.-R.C., C.-Y.C., K.-C.C. and C.-C.P.; Resources, C.-C.P.; Writing—Original Draft Preparation, Z.-C.M., W.C.C., L.-C.W. and Z.-J.Q.; Writing—Review & Editing, L.-C.W.; L.H.T., F.-Y.A. and K.-W.T.; Supervision, Z.-C.M. and W.C.C. Project Administration, L.-K.C.; Funding Acquisition, Z.-C.M. and W.-C.C. All authors have read and agreed to the published version of the manuscript.

DATA AVAILABILITY STATEMENT

The data underlying this article are available in the article.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

(See related article by Marques da Silva et al. The potential association between influenza vaccination and lower incidence of renal cell carcinoma. *Clin Kidney J* (2023) 16: 1714–1717.)

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