Hindawi
European Journal of Cancer Care
Volume 2023, Article ID 5036299, 9 pages
https://doi.org/10.1155/2023/5036299

Research Article

Susceptibility of Developing Renal and Lung Cancer in Polycystic Kidney Disease Patients: An Evidence in Reaching Consensus

Lung-Wen Tsai[1,2,3] **Chun-Ming Shih**[4,5] **Szu-Yuan Li**[6] **Sung-Hui Tseng**[7] **Rajni Dubey**[4] **and Mai-Szu Wu**[8,9]

[1]*Department of Medicine Research, Taipei Medical University Hospital, Taipei 11031, Taiwan*
[2]*Department of Information Technology Office, Taipei Medical University Hospital, Taipei 11031, Taiwan*
[3]*Graduate Institute of Data Science, College of Management, Taipei Medical University, Taipei 11031, Taiwan*
[4]*Division of Cardiology, Department of Internal Medicine, Taipei Medical University Hospital, Taipei 11031, Taiwan*
[5]*Department of Internal Medicine, School of Medicine, College of Medicine, Taipei Medical University, Taipei 11031, Taiwan*
[6]*Division of Nephrology, Department of Medicine, Taipei Veterans General Hospital, Taipei 112, Taiwan*
[7]*Department of Physical Medicine and Rehabilitation, Taipei Medical University Hospital, Taipei 11031, Taiwan*
[8]*TMU Research Center of Urology and Kidney, Taipei Medical University, Taipei 11031, Taiwan*
[9]*Division of Nephrology, Department of Internal Medicine, Taipei Medical University, Shuang Ho Hospital, New Taipei City 235, Taiwan*

Correspondence should be addressed to Rajni Dubey; 215195@h.tmu.edu.tw and Mai-Szu Wu; maiszuwu@gmail.com

Received 12 March 2023; Revised 30 July 2023; Accepted 21 August 2023; Published 29 August 2023

Academic Editor: Divakar Sharma

Objective. The association between Polycystic Kidney Disease (PKD) and susceptibility to developing oncogenicity states remains controversial, and no consensus has yet been reached. Large-scale studies on this association are also lacking. Therefore, we identified the risk of developing cancer in PKD patients. *Methods*. Patients diagnosed with PKD between 2000 and 2010 were enrolled in the National Health Insurance Research Database (NHIRD)-derived Longitudinal Health Insurance. Patients with antecedent cancer, end-stage renal disease, or those diagnosed with cancer within one year were excluded. Using a Standardized Incidence Ratio (SIR), we compared the patterns of cancer incidence in PKD patients and the general population. *Results*. The entire cohort was observed for 8,014 people, and a total of 1820 PKD patients were included, and after a median follow-up of 4.43 years, 82 patients developed cancer. Though the risk of overall cancers was comparable between PKD patients and the general population, the PKD patients exhibited a higher risk of kidney malignancy (SIR 3.72, 95% CI 1.60~7.33). The female PKD patients were at a higher risk of lung and mediastinal cancer (SIR: 2.83, 95% CI 1.03~6.16). The subgroup analysis revealed a significantly higher risk of kidney cancer in the patients aged <65 years (SIR 7.39, 95% CI 1.99~18.93) than those elderly patients, especially in the females (SIR 9.81, 95%1.10~35.41, $p < 0.05$). The multivariate analysis showed significant risk factors for cancer among the PKD population, including 1-year age (HR 1.04; 95% CI 1.02–1.06; $p < 0.001$), male gender (HR 1.85; 95% CI 1.14–3.00; $p = 0.012$), and chronic liver disease (HR 2.03; 95% CI 1.31–3.13; $p < 0.001$). *Conclusion*. PKD patients may be more susceptible to developing renal, lung, and mediastinal cancer than the control population, which might be attributed to PKD genetic instability.

1. Introduction

Polycystic Kidney Disease (PKD) is a common genetic disorder, occurring in approximately 1 in every 1000 live births [1]. It is characterized by the formation of multiple cysts in both kidneys, which further progress in size, leading to renal enlargement, insufficiency, and failure with extrarenal manifestations. PKD eventually results in dialysis and even renal transplantation as the ultimate treatment, and 50% of PKD patients progress to end-stage renal disease (ESRD). Furthermore, PKD patients have been reported to have a 1.6 to 3.2-fold relative mortality rate compared to the general

population [2]. The disease may also adversely impact the liver, pancreas, and colon leading to cardiac valvular defects and intracranial arterial aneurysms. PKD occurs in two forms, i.e., autosomal dominant (ADPKD) and autosomal recessive (ARPKD), in which ADPKD is caused by mutations in either of the two genes (PKD1) and (*PKD2*) encoding plasma membrane-spanning proteins polycystin 1 and polycystin 2, respectively [3], regulating tubular and vascular development in the kidneys and other organs.

In contrast, *PKHD1* has been identified as the major gene for ARPKD [4]. PKD proteins are confined to the cilial body, and renal cilia loss or abnormalities are associated with cyst development [5]. Although every cell in a heterozygous individual with autosomal dominant PKD carries a copy of the mutated *PKD* gene and a normal allele, renal cysts form only in a tiny fraction of the tubules, primarily the collecting ducts. It is believed that cyst formation occurs after an epithelial cell sustains a second genetic "hit" that compromises the function of the normal allele [6]. In contrast, the PKHD1 gene is highly expressed in fetal and adult kidneys and at lower levels in the liver [7].

Genomic instability is a term used to describe the acquisition of alterations in the genome, including chromosomal destabilization, gene amplification, and DNA-damaging agents associated with mutations. It has been proposed that genomic instability could be a driving force behind multistep carcinogenesis [8]. The DNA of patients with genomic instability is often more susceptible to mutagens than the general population [9]. As recent clinical and animal studies have reported PKD subjects with genomic instability [10–13], these patients may have a higher risk of developing the malignant disease. Therefore, we conducted a nationwide cohort study using the Taiwan National Health Insurance Research Database (NHIRD) to identify whether PKD patients are prone to developing the malignant disease.

2. Materials and Methods

2.1. Data Source. In this nationwide cohort study, we employed the Longitudinal Health Insurance Database (LHID) obtained from the NHIRD from 2000 to 2010 (Figure 1). Taiwan's National Health Insurance program was launched in 1995 and contains healthcare data of 23 million population comprising nearly 99% of Taiwan's population. The LHID consisted of 1 million beneficiaries randomly sampled from the original NHI beneficiaries, which consisted of deidentified secondary data ranging from demographic data to detailed orders from ambulatory and inpatient care. These data are released mainly for research purposes, comprising the entire registry, and claim data from this health insurance system. NHIRD has been comprehended as the basis for study in several research articles [14–16], and the accuracy of diagnoses based on this database has been validated previously for numerous diseases [17–20]. The disorders were coded according to the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes, 2001 edition. The study was approved by Taipei Medical University-Joint Institutional Review Board (TMU-JIRB) (No. N201710012) on 19th October 2017.

2.2. Study Subjects. During 1st January, 2000, and 31st December, 2010, the patients with at least twice ambulatory visit or hospitalization coding ICD-9 CM 753.1, 753.10, 753.12, 754.13, or 753.14 (coding for PKD) were enrolled. The exclusion criteria included patients under 18 years of age, ESRD, and a history or diagnosis of any cancer within the first year of the follow-up period. For analysis, we collected information such as comorbidities, including the Charlson comorbidity index score, diabetes mellitus, hypertension, chronic kidney disease, coronary artery disease, dyslipidemia, and chronic liver disease. Data regarding the residential area's monthly income and urbanization levels were obtained as a substitute for socioeconomic status. Times of ambulatory visits in the past year were also collected as a marker of healthcare utilization.

2.3. Outcomes. The Catastrophic Illness Registry was employed to identify patients who were diagnosed with cancer. Therefore, the endpoint of the current study was the incidence of any form of cancer. Pathohistological confirmation is required for a diagnosis of cancer to be reported in the Catastrophic Illness Registry. All patients were followed until the manifestation of cancer, a dropout from the NHI program, death, or the end of 2010.

2.4. Statistical Analysis. The risk of cancer among the patients with PKD was determined with the Standardized Incidence Ratio (SIR), which is defined as the ratio of observed to the expected cancer numbers. The expected number of cancer patients was estimated by adding up the national incidence rate of cancers according to age (in 5-year intervals), sex, and calendar year by the corresponding stratum-specific person-time accumulated in the cohort. The population of each age and sex strata for Taiwan was based on the population census 2001. Similarly, stratum-specific incidence rates were derived from the cancer registry data 2001. The 95% Confidence Intervals (CI) for the SIRs were estimated assuming the observed number of cancers followed a Poisson probability distribution. We used univariate and multivariate backward conditional Cox proportional hazards models to analyze the association between PKD and cancer and identify cancer development predictors among patients with PKD. Risk factors with a p value <0.1 were entered into the multivariate analysis. Microsoft SQL Server 2008 R2 (Microsoft Corp., Redmond, Washington, USA) was used for data linkage, processing, and sampling. All statistical analyses were conducted using STATA statistical software (version 12.0; StataCorp., Texas, USA). A p value <0.05 was considered statistically significant.

3. Results

3.1. Characteristics of the Study Population. For 10 years (2000–2010), the entire cohort was observed for 8,014 people and identified 1820 PKD patients meeting the inclusion criteria (Table 1). The mean age of patients at the time of diagnosis of PKD was 59.5 ± 17.5 years. Of these, the

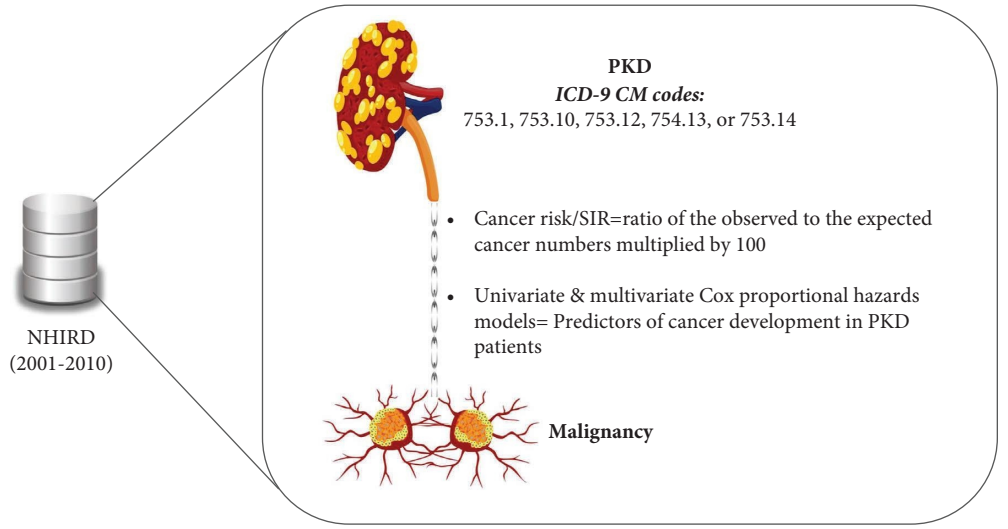

Figure 1: Study conceptual overview. To determine the association between PKD and the risk of malignancy, data were obtained from the NHIRD (year: 2000–2010). It was performed by investigating SIR, uni- and multivariate Cox proportional hazards model. NHIRD: National Health Insurance Research Database, ICD-9 CM: International Classification of Disease, Ninth Revision, Clinical Modification, SIR: Standard Incidence Rate, and PKD: Polycystic Kidney Disease.

Table 1: Characteristics of the study subjects.

	Total no. of patients (%)	No. of male patients (%)	No. of female patients (%)
No. of patient (%)	1,820	1,040 (57.1)	780 (42.9)
Person-year at risk	8,013	4,410	3,603
Age at diagnosis	59.5 ± 17.5	61.0 ± 16.7	57.5 ± 18.3
Median follow-up (year)	4.4 ± 3.0	4.2 ± 3.0	4.6 ± 3.2
Outpatient visits, (past 1 year)			
≦5 visits, *n* (%)	87 (4.8)	64 (6.2)	23 (2.9)
6–10 visits, *n* (%)	205 (11.3)	125 (12.0)	80 (10.3)
>10 visits, *n* (%)	1528 (84.0)	851 (81.8)	677 (86.8)
Income			
Dependent, *n* (%)	420 (23.1)	179 (17.2)	241 (30.9)
0–624 US dollars, *n* (%)	454 (24.9)	323 (31.1)	131 (16.8)
625–1,374 US dollars, *n* (%)	803 (44.1)	432 (41.5)	371 (47.6)
>1,375 US dollars, *n* (%)	143 (7.9)	106 (10.2)	37 (4.7)
Urbanization			
Level 1, *n* (%)	985 (54.1)	566 (54.4)	419 (53.7)
Level 2, *n* (%)	629 (34.6)	364 (35.0)	65 (8.3)
Level 3, *n* (%)	175 (9.6)	95 (9.1)	80 (10.3)
Level 4, *n* (%)	31 (1.7)	15 (1.4)	16 (2.1)
Charlson comorbidity index score			
0–2, *n* (%)	434 (23.8)	217 (20.9)	217 (27.8)
3-4, *n* (%)	372 (20.4)	210 (20.2)	162 (20.8)
≧5, *n* (%)	613 (33.7)	613 (58.9)	401 (51.4)
No. of comorbidities (%)			
Diabetes mellitus, *n* (%)	537 (29.5)	306 (29.4)	231 (29.6)
Hypertension, *n* (%)	1100 (60.4)	672 (64.6)	428 (54.9)
Chronic kidney disease, *n* (%)	557 (30.6)	342 (32.9)	215 (27.6)
Coronary artery disease, *n* (%)	718 (39.5)	420 (40.4)	298 (38.2)
Dyslipidemia, *n* (%)	637 (35.0)	377 (36.3)	260 (33.3)
Chronic liver disease, *n* (%)	624 (34.3)	383 (36.8)	241 (30.9)
Autoimmune disease, *n* (%)	240 (13.2)	115 (11.1)	125 (16.0)
Drug abuse, *n* (%)	46 (2.5)	35 (3.4)	11 (1.4)

majority of the patients were male (65.4%). The median follow-up was 4.4 ± 3.0 years.

3.2. Standardized Incidence Rates (SIR) of Cancer. During the follow-up period, 82 cancer cases were found. Compared with the general population, patients with PKD had a nonsignificant increase in their overall risk of cancer (SIR 1.20, 95% CI 0.95–1.49). However, the general PKD patients were found at a higher risk of developing renal malignancy (SIR 3.72, 95% CI 1.60~7.33), while female PKD patients, in particular, carry a higher risk of lung cancer (SIR 2.83, 95% CI 1.03~6.16) (Table 2).

In the subgroup analysis (Table 3), we found a significantly higher risk of kidney cancer in the patients aged <65 years (SIR 7.39, 95% CI 1.99~18.93) than those elderly patients, especially in the females (SIR 9.81, 95%1.10~35.41, $p < 0.05$). When stratified by duration of diagnosis of PKD, the SIRs were the highest after 1~3 years of diagnosis of PKD.

3.3. Risk Factors for Cancer in Patients with PKD. In multivariate analysis (Table 4), the significant risk factors for cancer among PKD population included the age of being one year older (HR 1.04; 95% CI 1.02–1.06; $p < 0.001$), male (HR 1.85; 95% CI 1.14–3.00; $p = 0.012$), and chronic liver disease (HR 2.03; 95% CI 1.31–3.13; $p < 0.001$). Neither hypertension nor comorbidity nor socioeconomic status influenced the risk of developing cancer in this population.

4. Discussion

So far, the clear evidence on pathological crosstalk between PKD and malignancy is inconclusive and debatable. This concern has also been raised by Cachat and Renella and advocated to investigating this association in populations younger than 20 years [21]. This might be attributed to the low prevalence of PKD and the lack of a powerful tool for screening. Studies have implied that PKD may be associated with renal cell carcinoma [22]. In a population-based cohort study, significantly higher risks of liver, colon, and kidney cancer have been documented [23]. A recent case report on 5 patients revealed the risk of hepatocellular carcinoma, testicular germ cell tumor, renal rhabdoid tumor, and perivascular epithelioid cell tumor [24]. However, our main findings showed that PKD patients are more likely to develop kidney cancer than the general population. In contrast, female PKD patients may have a higher risk of developing lung cancer than their normal counterparts. In PKD, ECM fibrotic remodeling accompanies cyst expansion and participates in progressive declining renal function [25]. The degree of fibrosis has been identified as the most critical manifestation associated with the progression to ESRD. Using Else Kröner-Fresenius Registry and histopathological registry for PKD, Jilg et al. showed that PKD patients may have a higher risk of renal cell carcinoma [26]. In another study, among 79 dialysis patients who required nephrectomy, patients with uremia caused by PKD had a 2~3 times higher risk of renal cell carcinoma than those with uremia caused by other etiologies [27]. However, the conclusion of these studies is limited by the small patient number in the dialysis population. End-stage renal disease (ESRD) is a well-established risk factor for renal cell carcinoma, especially when associated with acquired cystic kidney disease [28, 29]. In contrast to previous studies, we used a nationwide screening method to identify a large PKD population, excluding ESRD patients, to rule out the influence of dialysis and acquired cystic kidney disease. Our study provides relatively nonbiased data supporting PKD patients with a high risk of developing kidney malignancy.

Common pathological features of PKD include abnormal cell proliferation, disturbance of cell polarity along with dedifferentiation, extracellular matrix remodeling, and the development of interstitial fibrosis [30]. Some of these pathological changes share a similar mechanism of neoplasm formation, especially cell dedifferentiation and abnormal proliferation. The PKD corpus gene PKD1 is non-kidney-specific and has been recognized to exhibit a tumor regulation effect. PKD1 prevents tumor epithelial-mesenchymal change [31] and has been reported to regulate the malignant potential of human osteosarcoma negatively [32]. Notably, the downregulation of PKD1 in gastric carcinoma promotes invasive phenotype change and could result in a poor prognosis [33].

A notable finding in our study is a higher risk of developing lung cancer in female PKD patients (Figure 2). Though it is still unclear whether etiologic factors contributing to lung cancer differ in women and men; however, a stable incidence of age-adjusted lung cancer in females while a continued decrease in males has been observed [34, 35]. In female PKD patients, the pulmonary epithelial cell may be prone to genomic instability and developing lung neoplasm. Though epidemiological studies reported a 2-fold greater risk of developing kidney cancer in their lifetime in males than females [36], a study on a European cohort showed that the male-to-female ratio was almost equal in patients more than 70 years compared to a 2 : 1 ratio at ages 41–60 years [37], indicating a possible role of female hormones. Specifically, the physiological and hormonal alterations, such as increased estrogen levels, renal hyperfiltration, and weight gain, could also be attributed to the association of parity with kidney cancer.

Further, multivariate analysis showed a significant risk factor for cancer in the PKD population in males with an HR of 1.85. This result aligns with a previous study on 5654 renal cancer patients treated at ten international academic centers, in which females demonstrated a 19% reduced death risk compared to males (HR = 0.81) [38]. Experimental and clinical studies have shown that targeting estrogen/ERs signaling pathways might protect against certain renal disorders. Furthermore, in seminal research after inducing ischemia-reperfusion injury, females showed less severe renal functional impairment and reduced histologic damage [39]. This gender inconsistency may be ascribed to the protective impact of female hormones.

Besides, recent observational studies have strongly indicated that the risk of renal cell carcinoma (RCC) in chronic kidney disease (CKD) patients, particularly end-stage kidney

Table 2: SIR for cancers in PKD patients.

Site of cancers	Total			Male			Female		
	Observed	Expected	SIR (95% CI)	Observed	Expected	SIR (95% CI)	Observed	Expected	SIR (95% CI)
All cancers	82	68.53	1.20 (0.95–1.49)	59	46.56	1.27 (0.96–1.63)	23	21.97	1.05 (0.66–1.57)
Head and neck	5	5.45	0.92 (0.30–2.14)	4	4.88	0.82 (0.22–2.10)	1	0.57	1.76 (0.02–9.77)
Digestive	33	27.84	1.19 (0.82–1.67)	27	20.09	1.34 (0.89–1.96)	6	7.75	0.77 (0.28–1.69)
Esophagus	1	1.52	0.66 (0.01–3.67)	0	1.42	—	1	0.09	10.83 (0.14–60.24)
Stomach	4	3.64	1.10 (0.30–2.81)	4	2.68	1.49 (0.40–3.82)	0	0.96	—
Colon & rectum	11	10.34	1.06 (0.53–1.90)	8	6.96	1.15 (0.50–2.27)	3	3.38	0.89 (0.18–2.59)
Biliary tract	15	10.57	1.42 (0.79–2.34)	13	7.86	1.65 (0.88–2.83)	2	2.72	0.74 (0.08–2.66)
Pancreas	1	1.37	0.73 (0.01–4.07)	1	0.91	1.10 (0.01–6.10)	0	0.46	—
Lung & mediastinum	15	8.59	1.75 (0.98–2.88)	9	6.48	1.39 (0.63–2.64)	6	2.12	**2.83 (1.03–6.16)***
Bone & soft tissue	0	1.70	—	0	1.16	—	0	0.54	—
Skin	1	2.15	0.47 (0.01–2.59)	1	1.33	0.75 (0.01–4.17)	0	0.81	—
Breast	2	3.79	0.53 (0.06–1.91)	0	0.04	0.00 (88.32)	2	3.75	0.53 (0.06–1.93)
Genitourinary	18	11.37	1.58 (0.94–2.50)	13	7.6	1.71 (0.91–2.93)	5	3.77	1.32 (0.43–3.09)
Cervix	0	1.25	—	0	0	—	0	1.25	—
Uterus	1	0.66	1.51 (0.02–8.43)	0	0	—	1	0.66	1.51 (0.02–8.43)
Ovary	0	0.50	—	0	0	—	0	0.5	—
Prostate	6	4.51	1.33 (0.49–2.90)	6	4.51	1.33 (0.49–2.90)	0	0	—
Bladder	3	2.08	1.44 (0.29–4.22)	3	1.64	1.83 (0.37–5.34)	0	0.44	—
Kidney	8	2.15	**3.72 (1.60–7.33)***	4	1.31	3.04 (0.82–7.79)	4	0.84	**4.78 (1.29–12.25)***
CNS	0	0.41	—	0	0.27	—	0	0.14	—
Thyroid	2	0.88	2.28 (0.26–8.25)	0	0.27	—	2	0.6	3.31 (0.37–11.97)
Hematologic malignancies	4	5.47	0.73 (0.20–1.87)	3	3.68	0.82 (0.16–2.38)	1	1.79	0.56 (0.01–3.10)
All others	2	0.89	2.25 (0.25–8.12)	2	0.76	2.64 (0.30–9.54)	0	0.13	—

SIR, Standardized Incidence Ratio; PKD, Polycystic Kidney Disease; CI, Confidence Interval; CNS Central Nervous System. $^{*}p < 0.05$. Bold values have * symbol indicating significant $p < 0.05$.

Table 3: SIR for cancers stratified by age and PKD duration.

Site of cancers	Total			Male			Female		
	Obs.	Exp.	SIR (95% CI)	Obs.	Exp.	SIR (95% CI)	Obs.	Exp.	SIR (95% CI)
By age									
Age < 65 years									
All cancers	31	21.28	1.46 (0.99–2.07)	20	12.6	1.59 (0.97–2.45)	11	8.68	1.27 (0.63–2.27)
Lung & mediastinum	5	1.73	2.89 (0.93–6.74)	2	1.13	1.78 (0.20–6.41)	3	0.61	**4.96 (1.00–14.48)***
Kidney	4	0.54	**7.39 (1.99–18.93)***	2	0.34	5.93 (0.67–21.41)	2	0.2	**9.81 (1.10–35.41)***
Age ≧ 65 years									
All cancers	51	47.25	1.08 (0.80–1.42)	39	33.96	1.15 (0.82–1.57)	12	13.3	0.90 (0.47–1.58)
Lung & mediastinum	10	6.86	1.46 (0.70–2.68)	7	5.35	1.31 (0.52–2.70)	3	1.51	1.98 (0.40–5.79)
Kidney	4	1.61	2.49 (0.67–6.36)	2	0.98	2.05 (0.23–7.39)	2	0.63	3.16 (0.36–11.42)
By duration of diagnosis of PKD									
Duration < 1 year									
All cancers	63	54.21	1.16 (0.89–1.49)	43	36.82	1.17 (0.84–1.57)	20	17.39	1.15 (0.70–1.78)
Lung & mediastinum	13	6.72	**1.93 (1.03–3.31)***	7	5.05	1.39 (0.56–2.86)	6	1.67	**3.60 (1.31–7.83)***
Kidney	3	1.74	1.73 (0.35–5.05)	1	1.07	0.94 (0.01–5.20)	2	0.67	3.00 (0.34–10.82)
Duration 1–3 years									
All cancers	49	37.38	1.31 (0.97–1.73)	37	25.38	1.46 (1.03–2.01)*	12	12	1.00 (0.52–1.75)
Lung & mediastinum	10	4.81	**2.08 (1.00–3.82)***	7	3.64	1.92 (0.77–3.96)	3	1.17	2.56 (0.51–7.48)
Kidney	7	1.13	**6.19 (2.48–12.75)***	4	0.68	5.90 (1.59–15.11)*	3	0.45	**6.61 (1.33–19.33)***

SIR, Standardized Incidence Ratio; PKD, Polycystic Kidney Disease; CI, Confidence Interval; CNS Central Nervous System. * $p < 0.05$. Bold values have * symbol indicating $p < 0.05$.

Table 4: Risk factors for cancer in patients with PKD.

Variables	Univariate analysis		Multivariate analysis[a]	
	HR (95% CI)	p	HR (95% CI)	p value
Age[b]	1.04 (1.03–1.06)	<0.001	1.04 (91.02–1.06)	<0.001
Male	2.06 (1.27–3.34)	0.003	1.85 (1.14–3.00)	0.012
Charlson comorbidity index score[c]	1.13 (1.05–1.23)	0.002		
Diabetes mellitus	2.10 (1.35–3.25)	0.001		
Hypertension	2.08 (1.27–3.39)	0.003		
Chronic kidney disease	0.95 (0.58–1.54)	0.825		
Coronary artery disease	2.14 (1.38–3.30)	0.001		
Dyslipidemia	1.68 (1.09–2.61)	0.020		
Chronic liver disease	2.19 (1.42–3.39)	<0.001	2.03 (1.31–3.13)	0.001
Autoimmune disease	1.18 (0.63–2.23)	0.604		
Drug abuse	2.17 (0.68–6.91)	0.189		
Outpatient visits, (past 1 year)				
≦5 visits	1			
6–10 visits	0.72 (0.17–3.02)	0.656		
>10 visits	1.39 (0.44–4.41)	0.575		
Incoming				
Dependent	1			
NT 0–19,100	0.90 (0.48–1.67)	0.739		
NT 19,100–42,000	0.98 (0.57–1.68)	0.944		
>NT 42,000	0.40 (0.12–1.35)	0.139		
Urbanization				
Level 1	1			
Level 2	1.15 (0.72–1.83)	0.552		
Level 3	1.10 (0.52–2.33)	0.809		
Level 4	Not available			

PKD, Polycystic Kidney Disease; 95% CI, 95% Confidence Interval; HR, Hazards Ratio; [a]all factors with $p < 0.1$ on univariate analyses were included in the Cox multivariate analysis. [b]HR for being 1 year older. [c]HR for being 1 score more.

disease (ESKD), is approximately 3–7 times higher than in the general population. The precise mechanism of renal insufficiency transforming healthy kidney cells into tumor cells remains unknown. Reportedly, CKD may lead to RCC through underlying cystic disease or oxidative stress mechanisms. Conversely, RCC can contribute to the development of CKD due to factors such as the tumor itself, surgical reduction of renal mass (partial or radical nephrectomy), and perioperative acute kidney injury. Therefore, the relationship between CKD and RCC is complex,

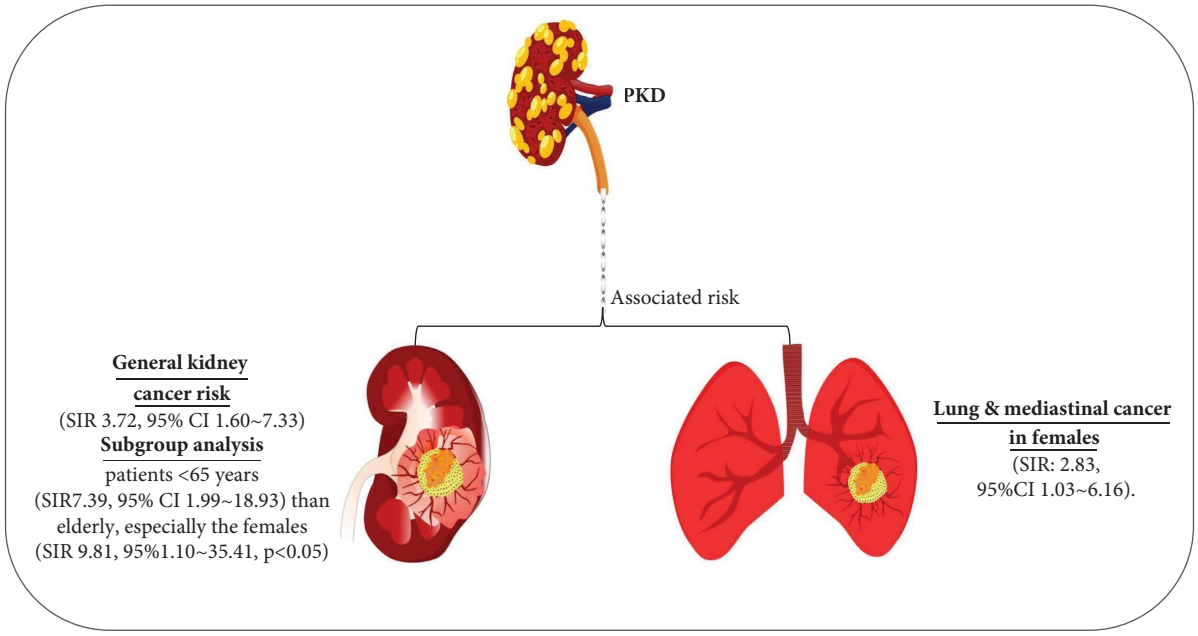

Figure 2: Study outcomes revealing kidney and lung/mediastinal cancer risk in PKD patients.

bidirectional, and multifactorial. The hypothesis suggests that various factors, such as chronic inflammation related to uremia, oxidative stress, retention of uremic toxins and solutes, compromised immune function, the dialysis procedure, exposure to medications and toxins, as well as the presence of comorbid conditions, collectively contributing to an elevated risk of several cancers, including RCC [40–42].

Apart from several strengths, our study also has some limitations. Firstly, the Taiwan NHIRD does not offer detailed personal history and lifestyle information, such as smoking habits, body mass index, and functional capacity, which may impact PKD characteristics. Therefore, in addition to generating significant and noteworthy associations, our study might encounter detection or Berkson bias leading to spurious confounding factors caused by conditional factors such as an increased probability of receiving kidney ultrasound/computed tomography exam or hospitalization rate in PKD patients compared to the general population [43]. Secondly, all the data used in this study have been recorded with ICD-9-CM codes, making it infeasible to classify disease status further or determine disease lesions. Thirdly, the NHIRD does not include laboratory data, which could have been valuable for our analysis. Fourthly, we did not investigate the incidence of cerebral vascular accidents in ADPKD patients. Lastly, we did not analyze the impact of medications, such as renin-angiotensin-aldosterone system blockades and statins, on PKD patients.

5. Conclusions

Our investigation revealed that overall PKD patients are prone to develop kidney cancer, while female PKD patients may have a higher risk of lung and mediastinal cancer. Patients aged <65 may be at a higher risk of kidney cancer than elderly patients, particularly females. However, further extensive research is needed to reach a consensus and validate the hypothesis through elucidating underlying mechanisms.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

The authors acknowledge the support of Taipei Medical University Hospital, Taiwan (Grant no.: 109TMUH-SP-03).

References

[1] M. R. Eccles and C. A. Stayner, "Polycystic kidney disease-where gene dosage counts," *F1000prime reports*, vol. 6, p. 24, 2014.

[2] K. W. Florijn, W. M. Noteboom, J. L. van Saase, P. C. Chang, M. H. Breuning, and J. P. Vandenbroucke, "A century of mortality in five large families with polycystic kidney disease," *American Journal of Kidney Diseases*, vol. 25, no. 3, pp. 370–374, 1995.

[3] P. C. Harris, "Molecular basis of polycystic kidney disease: PKD1, PKD2 and PKHD1," *Current Opinion in Nephrology and Hypertension*, vol. 11, no. 3, pp. 309–314, 2002.

[4] C. Bergmann, "Genetics of autosomal recessive polycystic kidney disease and its differential diagnoses," *Front Pediatr.*, vol. 5, p. 221, 2017.

[5] P. C. Harris, "2008 Homer W. Smith award: insights into the pathogenesis of polycystic kidney disease from gene discovery," *Journal of the American Society of Nephrology*, vol. 20, no. 6, pp. 1188–1198, 2009.

[6] F. Qian and T. J. Watnick, "Somatic mutation as mechanism for cyst formation in autosomal dominant polycystic kidney disease," *Molecular Genetics and Metabolism*, vol. 68, no. 2, pp. 237–242, 1999.

[7] Y. Nagasawa, S. Matthiesen, L. F. Onuchic et al., "Identification and characterization of Pkhd1, the mouse orthologue of the human ARPKD gene," *Journal of the American Society of Nephrology*, vol. 13, no. 9, pp. 2246–2258, 2002.

[8] J. Breivik and G. Gaudernack, "Genomic instability, DNA methylation, and natural selection in colorectal carcinogenesis," *Seminars in Cancer Biology*, vol. 9, no. 4, pp. 245–254, 1999.

[9] M. B. Schabath, M. R. Spitz, H. B. Grossman et al., "Genetic instability in bladder cancer assessed by the comet assay," *JNCI Journal of the National Cancer Institute*, vol. 95, no. 7, pp. 540–547, 2003.

[10] M. Li, S. Qin, L. Wang, and J. Zhou, "Genomic instability in patients with autosomal-dominant polycystic kidney disease," *Journal of International Medical Research*, vol. 41, no. 1, pp. 169–175, 2013.

[11] L. Battini, S. Macip, E. Fedorova et al., "Loss of polycystin-1 causes centrosome amplification and genomic instability," *Human Molecular Genetics*, vol. 17, no. 18, pp. 2819–2833, 2008.

[12] S. Burtey, M. Riera, E. Ribe et al., "Centrosome overduplication and mitotic instability in PKD2 transgenic lines," *Cell Biology International*, vol. 32, no. 10, pp. 1193–1198, 2008.

[13] W. A. AbouAlaiwi, S. Ratnam, R. L. Booth, J. V. Shah, and S. M. Nauli, "Endothelial cells from humans and mice with polycystic kidney disease are characterized by polyploidy and chromosome segregation defects through survivin down-regulation," *Human Molecular Genetics*, vol. 20, no. 2, pp. 354–367, 2011.

[14] K. L. Wang, C. J. Liu, T. F. Chao et al., "Statins, risk of diabetes, and implications on outcomes in the general population," *Journal of the American College of Cardiology*, vol. 60, no. 14, pp. 1231–1238, 2012.

[15] C. Y. Wu, Y. J. Chen, H. J. Ho et al., "Association between nucleoside analogues and risk of hepatitis B virus-related hepatocellular carcinoma recurrence following liver resection," *JAMA*, vol. 308, no. 18, pp. 1906–1914, 2012.

[16] S. M. Ou, Y. T. Chen, P. W. Chao et al., "Nonsteroidal anti-inflammatory drug use is associated with cancer risk reduction in chronic dialysis patients," *Kidney International*, vol. 84, no. 1, pp. 198–205, 2013.

[17] U. Lindblad, L. Rastam, J. Ranstam, and M. Peterson, "Validity of register data on acute myocardial infarction and acute stroke: the Skaraborg Hypertension Project," *Scandinavian Journal of Social Medicine*, vol. 21, no. 1, pp. 3–9, 1993.

[18] C. C. Lin, M. S. Lai, C. Y. Syu, S. C. Chang, and F. Y. Tseng, "Accuracy of diabetes diagnosis in health insurance claims data in Taiwan," *Journal of the Formosan Medical Association*, vol. 104, no. 3, pp. 157–163, 2005.

[19] C. Y. Wu, F. K. Chan, M. S. Wu et al., "Histamine2-receptor antagonists are an alternative to proton pump inhibitor in patients receiving clopidogrel," *Gastroenterology*, vol. 139, no. 4, pp. 1165–1171, 2010.

[20] C. L. Cheng, Y. H. Kao, S. J. Lin, C. H. Lee, and M. L. Lai, "Validation of the national health insurance research database with ischemic stroke cases in taiwan," *Pharmacoepidemiology and Drug Safety*, vol. 20, no. 3, pp. 236–242, 2011.

[21] F. Cachat and R. Renella, "Risk of cancer in patients with polycystic kidney disease," *The Lancet Oncology*, vol. 17, no. 11, p. e474, 2016.

[22] D. S. Keith, V. E. Torres, B. F. King, H. Zincki, and G. M. Farrow, "Renal cell carcinoma in autosomal dominant polycystic kidney disease," *Journal of the American Society of Nephrology*, vol. 4, no. 9, pp. 1661–1669, 1994.

[23] T. M. Yu, Y. W. Chuang, M. C. Yu et al., "Risk of cancer in patients with polycystic kidney disease: a propensity-score matched analysis of a nationwide, population-based cohort study," *The Lancet Oncology*, vol. 17, no. 10, pp. 1419–1425, 2016.

[24] B. D. Friend, K. Wolfe Schneider, T. Garrington et al., "Is polycystic kidney disease associated with malignancy in children?" *Mol Genet Genomic Med.*, vol. 7, Article ID e00725, 2019.

[25] J. Norman, "Fibrosis and progression of autosomal dominant polycystic kidney disease (ADPKD)," *Biochimica et Biophysica Acta- Molecular Basis of Disease*, vol. 1812, no. 10, pp. 1327–1336, 2011.

[26] C. A. Jilg, V. Drendel, J. Bacher et al., "Autosomal dominant polycystic kidney disease: prevalence of renal neoplasias in surgical kidney specimens," *Nephron Clinical Practice*, vol. 123, no. 1-2, pp. 13–21, 2013.

[27] P. Hajj, S. Ferlicot, W. Massoud et al., "Prevalence of renal cell carcinoma in patients with autosomal dominant polycystic kidney disease and chronic renal failure," *Urology*, vol. 74, no. 3, pp. 631–634, 2009.

[28] M. D. Denton, C. C. Magee, C. Ovuworie et al., "Prevalence of renal cell carcinoma in patients with ESRD pre-transplantation: a pathologic analysis," *Kidney International*, vol. 61, no. 6, pp. 2201–2209, 2002.

[29] M. D. Hughson, D. Buchwald, and M. Fox, "Renal neoplasia and acquired cystic kidney disease in patients receiving long-term dialysis," *Archives of Pathology & Laboratory Medicine*, vol. 110, no. 7, pp. 592–601, 1986.

[30] E. Higashihara, S. Horie, S. Muto, T. Mochizuki, S. Nishio, and K. Nutahara, "Renal disease progression in autosomal dominant polycystic kidney disease," *Clinical and Experimental Nephrology*, vol. 16, no. 4, pp. 622–628, 2012.

[31] L. I. Bastea, H. Doppler, B. Balogun, and P. Storz, "Protein kinase D1 maintains the epithelial phenotype by inducing a DNA-bound, inactive SNAI1 transcriptional repressor complex," *PLoS One*, vol. 7, no. 1, Article ID e30459, 2012.

[32] Y. Onishi, T. Kawamoto, K. Kishimoto et al., "PKD1 negatively regulates cell invasion, migration and proliferation ability of human osteosarcoma," *International Journal of Oncology*, vol. 40, no. 6, pp. 1839–1848, 2012.

[33] M. Y. Shabelnik, L. M. Kovalevska, M. Y. Yurchenko, L. M. Shlapatska, Y. Rzepetsky, and S. P. Sidorenko, "Differential expression of PKD1 and PKD2 in gastric cancer and analysis of PKD1 and PKD2 function in the model system," *Experimental Oncology*, vol. 33, no. 4, pp. 206–211, 2011.

[34] J. B. Fu, T. Y. Kau, R. K. Severson, and G. P. Kalemkerian, "Lung cancer in women: analysis of the national Surveillance, Epidemiology, and End Results database," *Chest*, vol. 127, no. 3, pp. 768–777, 2005.

[35] L. Thomas, L. A. Doyle, and M. J. Edelman, "Lung cancer in women: emerging differences in epidemiology, biology, and therapy," *Chest*, vol. 128, no. 1, pp. 370–381, 2005.

[36] A. J. Peired, R. Campi, M. L. Angelotti et al., "Sex and gender differences in kidney cancer: clinical and experimental evidence," *Cancers*, vol. 13, no. 18, p. 4588, 2021.

[37] M. N. Hew, R. Zonneveld, I. P. Kümmerlin, D. Opondo, J. J. de la Rosette, and M. P. Laguna, "Age and gender related differences in renal cell carcinoma in a European cohort," *The Journal of Urology*, vol. 188, no. 1, pp. 33–38, 2012.

[38] E. N. Rampersaud, T. Klatte, G. Bass et al., "The effect of gender and age on kidney cancer survival: younger age is an independent prognostic factor in women with renal cell carcinoma," *Urologic Oncology: Seminars and Original Investigations*, vol. 32, no. 1, pp. 30.e9–13, 2014.

[39] J. Neugarten and L. Golestaneh, "Female sex reduces the risk of hospital-associated acute kidney injury: a meta-analysis," *BMC Nephrology*, vol. 19, no. 1, p. 314, 2018.

[40] P. H. Weng, K. Y. Hung, H. L. Huang, J. H. Chen, P. K. Sung, and K. C. Huang, "Cancer-specific mortality in chronic kidney disease: longitudinal follow-up of a large cohort," *Clinical Journal of the American Society of Nephrology*, vol. 6, no. 5, pp. 1121–1128, 2011.

[41] C.-Y. Chen, Y.-M. Liao, W.-M. Tsai, and H.-C. Kuo, "Upper urinary tract urothelial carcinoma in eastern taiwan: high proportion among all urothelial carcinomas and correlation with chronic kidney disease," *Journal of the Formosan Medical Association*, vol. 106, no. 12, pp. 992–998, 2007.

[42] L. Jørgensen, I. Heuch, T. Jenssen, and B. K. Jacobsen, "Association of albuminuria and cancer incidence," *Journal of the American Society of Nephrology*, vol. 19, no. 5, pp. 992–998, 2008.

[43] Y. T. Wu and H. Y. Lee, "National Health Insurance database in Taiwan: a resource or obstacle for health research?" *European Journal of Internal Medicine*, vol. 31, pp. e9–e10, 2016.