
بسم الله الرحمن الرحیم

Pediatric kidney disease and cancer:
a troubling connection

Masoumeh Mohkam, MD

Professor of Pediatric Nephrology

SBMU, Summer 2019

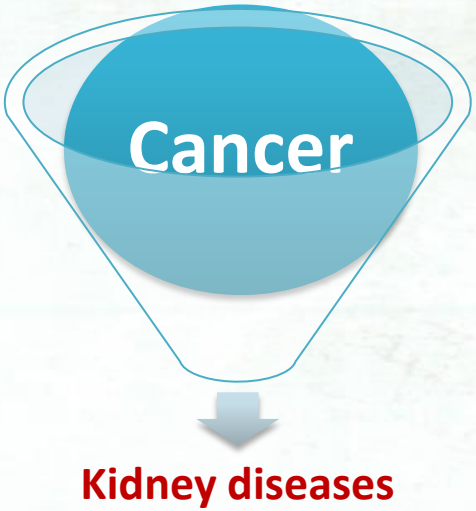
Pediatric kidney disease and cancer: a troubling connection

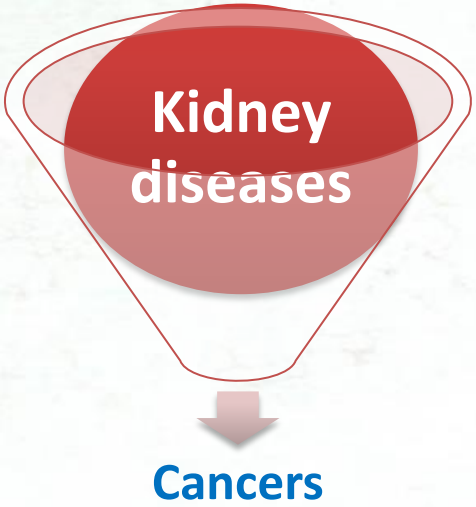
Chronic kidney disease (CKD) and cancer are connected in a number of ways in **both directions:**

Cancer can cause CKD either directly or indirectly through the adverse effects of therapies; **CKD may, conversely, be a risk factor for cancer**

Childhood Cancer Survivors (CCS)

Childhood Kidney diseases Survivors (CKS)





Late renal toxicity of treatment for childhood malignancy

Pediatric and adult nephrologists and oncologists involved in long-term follow-up of childhood cancer survivors (CCS) encounter many patients with chronic glomerular and/or renal tubular impairment.

Chronic nephrotoxicity

Childhood Cancer Survivor Study of >10,000 CCS treated in the reported that **0.5%** had developed renal failure or were requiring dialysis by a mean age of 27 years

Representing a **nine-fold** increased risk compared with their siblings

Oeffinger KC. N Engl J Med. 2006;355:1572–1582

Causes of chronic renal damage in CCS

- **Damage of malignant disease**

  Tumor infiltration, Obstruction
- **Long term sequelae of TLS**
- **Chemotherapy**

  ifosfamide, cisplatin, carboplatin, high-dose methotrexate, high-dose cyclophosphamide
- **Radiotherapy**
- **Surgery** (Nephrectomy, …)
- **Immunotherapy**
- **Antibiotics**
- **Hyperfiltration**

Glomerular dysfunction

The highest risks were observed with larger cumulative doses of ifosfamide and cisplatin (especially >500 mg/m^2) and with nephrectomy (especially in survivors older at the time of nephrectomy) and kidney radiotherapy.

Mulder RL. Cancer Epidemiol Biomark Prev. 2013;22:1736–1746.

Chronic glomerular and tubular nephrotoxicity

Adolescence	Children	
20-25%	20-50%	ifosfamide
10-30%	60-80%	cisplatin

Roderick Skinner. Pediatr Nephrol. 2018; 33(2): 215–225.

Chronic ifosfamide nephrotoxicity

Significant chronic ifosfamide nephrotoxicity appears to be common in adults, with **45%** (1-year survivors) and **53%** (5-year survivors) with **CKD stage ≥3** in a large cohort study

Stöhr W, Pediatr Blood Cancer. 2007;48:571–576.

Chronic cisplatin nephrotoxicity

Significant chronic ifosfamide nephrotoxicity appears to be common in adults, with **29%** (1-year survivors) and **33%** (5-year survivors) with **CKD stage ≥3** in a large cohort study

Latcha S, Clin J Am Soc Nephrol. 2016;11:1173–1179.

Chronic radiation nephropathy

may present with:

- Proteinuria
- Hypertension
- Reduced GFR, which may be progressive (observed in **46%** of adults who received 20 Gy radiotherapy exposing the left kidney during treatment for peptic ulcer disease)

Dawson LA. Int J Radiation Oncology Biol Phys. 2010;76:S108–S115
Luxton RW. Lancet. 1961;ii:1221–1224.

European Journal of Cancer
Volume 64, September 2016, Pages 52-61

Original Research

Long-term risk of renal and urinary tract diseases in childhood cancer survivors: A population-based cohort study

Trine Gade Bonnesen [a], Jeanette F. Winther [b], Peter H. Asdahl [a], Sofie de Fine Licht [b], Thorgerdur Gudmundsdottir [b], Anna Sällfors Holmqvist [c], Laura-Maria Madanat-Harjuoja [d, e], Laufey Tryggvadottir [f, g], Finn Wesenberg [h], Henrik Birn [i], Jørgen H. Olsen [b], Henrik Hasle [a], the ALiCCS study group

Denmark, Finland, Sweden, Norway

32,519 one-year survivors of childhood cancer for since 1950

1645 had urinary tract diseases and CKD (**RR=2.5** and AER 229/100000 person-year

Neuroblastoma, Hepatic and Renal tumors experienced the highest RRs.

EJC
EUROPEAN JOURNAL OF CANCER

Adult Life after Childhood Cancer in Scandinavia: Diabetes mellitus following treatment for cancer in childhood

Eur J Cancer. 2014;50(6):1169-75

Anna Sällfors Holmqvist[a,*], Jørgen H. Olsen[b], Klaus Kaae Andersen[b], Sofie de Fine Licht[b], Lars Hjorth[a], Stanislaw Garwicz[a], Christian Moëll[a], Harald Anderson[c], Finn Wesenberg[d], Laufey Tryggvadottir[e], Nea Malila[f], John D. Boice Jr.[g,h], Henrik Hasle[i], Jeanette Falck Winther[b] on behalf of the ALiCCS study group

Childhood cancer survivors are at increased risk for DM and its complications (Kidney problems and ……)

DM was diagnosed in 496 childhood cancer survivors, an AER (Absolute excess risks) of 43 per 100,000 person-years

The relative risks for DM were significantly increased after:

Wilms' tumor

Leukemia

CNS neoplasms

Germ-cell neoplasms

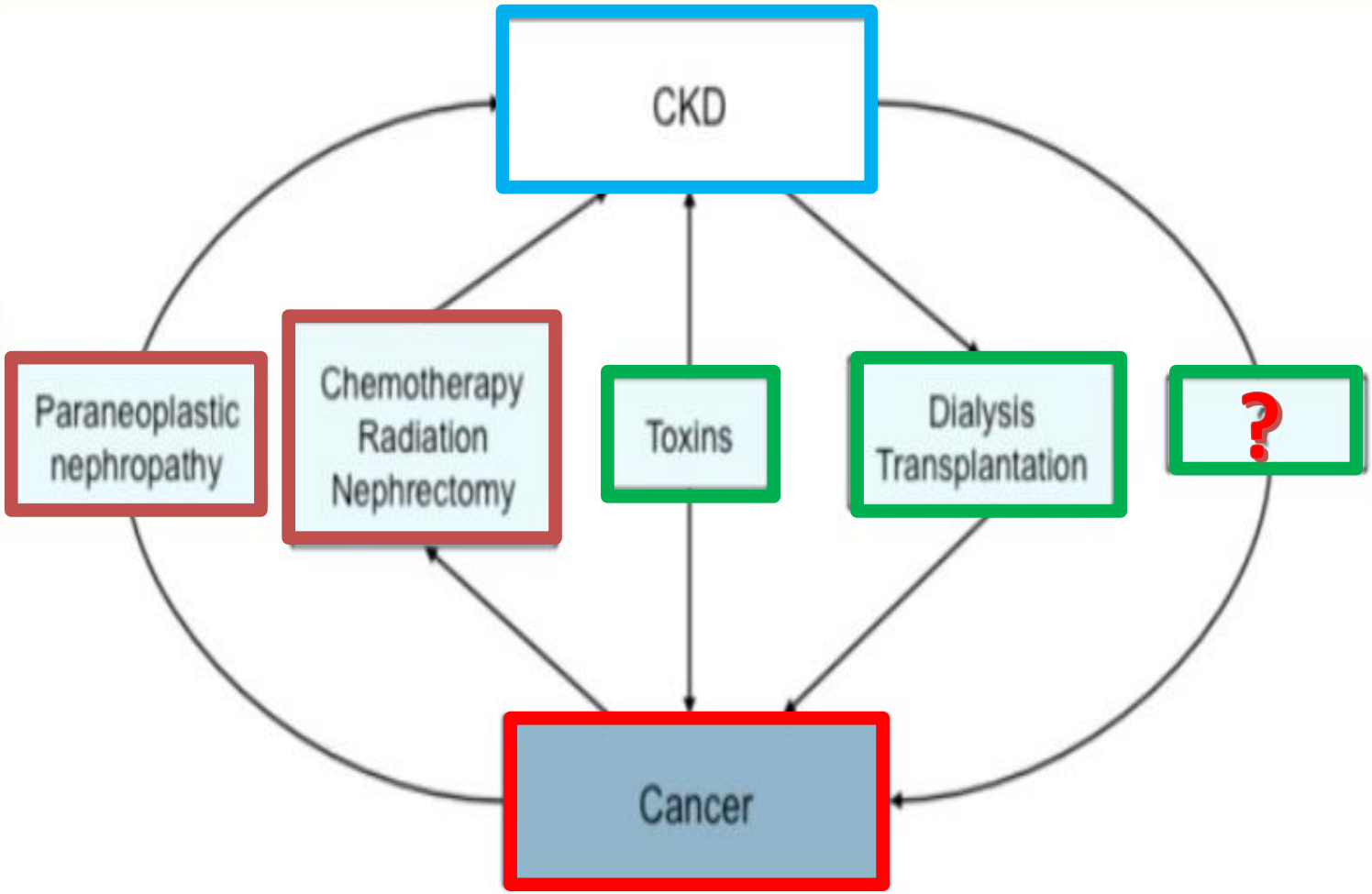
Malignant bone tumors

Hodgkin's lymphoma

The risk for DM type 2 was slightly higher than that for type 1.

Pediatric kidney diseases and risk of malignancies

Various pathways linking CKD and cancer



Pediatric ESRD (RRT)

Pediatric ESRD is associated with an increased risk of malignancies

Dialysis

Transplantation

ELSEVIER

Transplantation Proceedings

Volume 50, Issue 5, June 2018, Pages 1264-1271

Milestones in Transplantation

Kidney transplantation

Pediatric Renal Transplantation: Evaluation of Long-Term Outcomes and Comparison to Adult Population

Portugal

H. Antunes, B. Parada, E. Tavares-da-Silva, J. Carvalho, C. Bastos, A. Roseiro, P. Nunes, A. Figueiredo

101 pediatric patients **1981-2016**

Post-transplantation malignancies (incidence)	**Pediatric: 1%**	**Adults:5%**

Causes of Death in Pediatric kidney Transplantation

Malignancy	1 (8.3)
Infections	2 (16.7)
Cardiovascular	4 (33.3)
Unknown	3 (25.0)
Others	2 (16.7)

Transplantation Proceedings, Volume 50, Issue 5, 2018,1264-1271

Transplantation Proceedings
Volume 51, Issue 5, June 2019, Pages 1579-1584

17th Luso-Brazilian Congress of Transplantation and the 14th Portugese Congress of Transplantation
Renal transplantation

Pediatric Kidney Transplantation: Experience of a Center Over 4 Decades

111 pediatric renal Tx

Carolina Cordinhã [a], Luís Rodrigues [b, c], Carmen Carmo [a], Clara Gomes [a], Fernando Macário [b, c], A. Jorge Correia [a], Rui Alves [b, c], Arnaldo Figueiredo [c, d]

Age of recipient	< 11 yr	> 11 yr
Post-transplantation malignancy	-	3

Kidney Transplantation

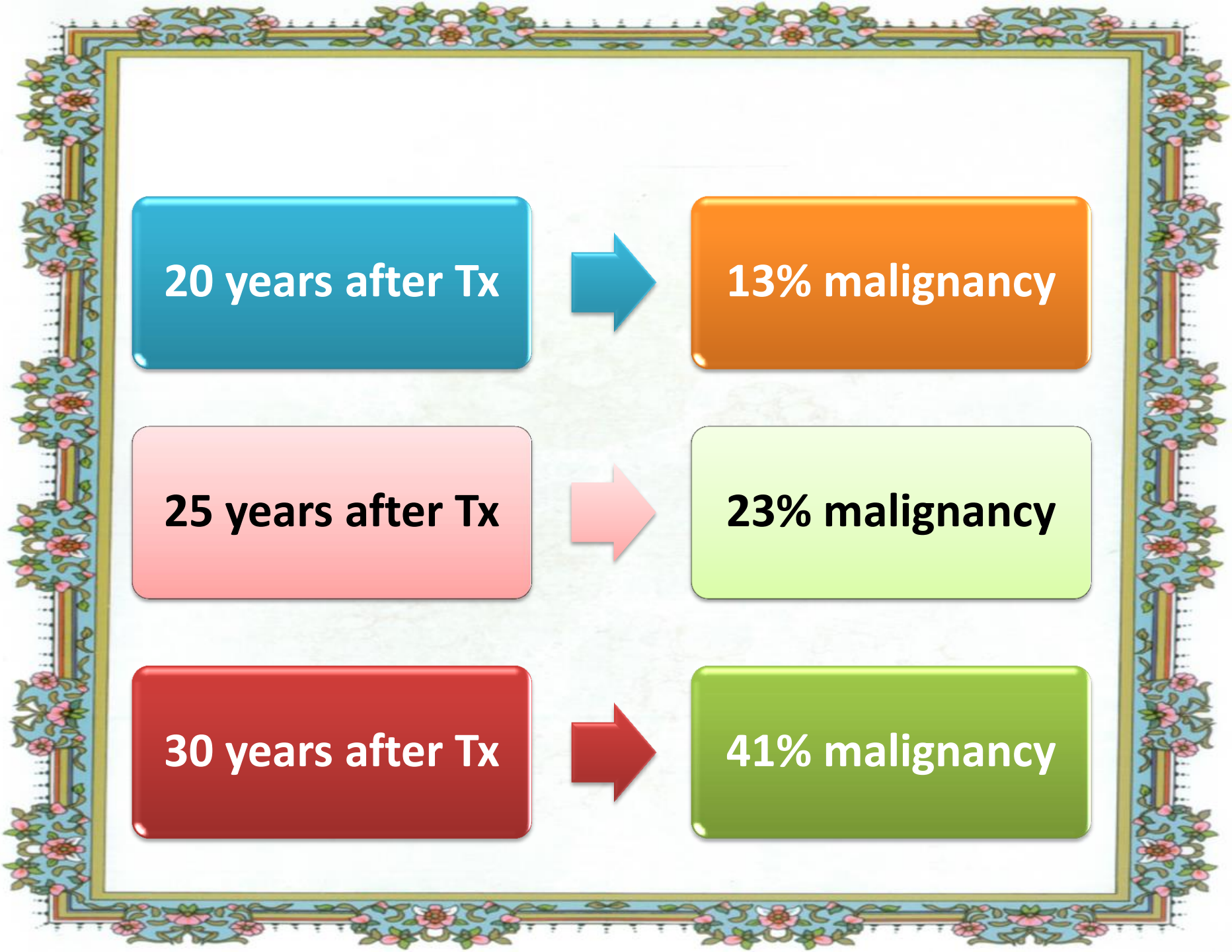
- Cancer is highly prevalent among patients with **pediatric ESRD after 25.3 years of transplantation**, with a high rate of recurrence.
- In **5709 Pt-yr F/U**, After a median of **25.3 years** of transplantation and at a median age of 33.5 years old, **105** primary malignancies had occurred in **54 of 249** patients.
- Cumulative incidence competing risk analysis showed that, after **30 years of transplantation, 41% of the survivors had developed cancer; 31% had developed a second *de novo* cancer <1 year after** initial cancer diagnosis.
- Among them, **cutaneous squamous cell carcinoma** was most frequent.

Amstel S, Clin J Am Soc Nephrol. 2015 Dec 7; 10(12): 2198–2204 (Amsterdam).

- The probability of developing a malignancy was **17%** (95% confidence interval [95% CI], 9% to 24%) after these children reached an age between **20 and 40** years old

- **10** times increase in the incidence of *de novo* malignancy compared with the general population

Coutinho HM, Arch Dis Child 85: 2001;478–483


20 years after Tx
13% malignancy
25 years after Tx
23% malignancy
30 years after Tx
41% malignancy

CJASN™

Clin J Am Soc Nephrol. 2015 Dec 7; 10(12): 2198–2204.
Published online 2015 Oct 1. doi: 10.2215/CJN.03630415

PMCID: PMC4670765
PMID: 26430089

Long-Term Risk of Cancer in Survivors of Pediatric ESRD

Sophie Ploos van Amstel,* Judith L. Vogelzang,* Marcus V. Starink,† Kitty J. Jager,‡ and Jaap W. Groothoff*

Amsterdam

Characteristics	LERIC Study Cohort	Range	Percentage
All patients			
No. of patients starting RRT	249		
Median age (yr) of survivors in 2010	39.9	20.9–52.4	
Median age (yr) at start of RRT	11.2	1.9–15.0	
Median time (yr) on RRT	25.3	0.3–39.3	
Median time (yr) with transplant	19.7	0.0–39.3	
Median time (yr) on dialysis	5.6	0.0–36.5	
Deaths			
No. of deaths	95		38.2
Median age (yr) at death	22.7	4.2–46.3	
Median time (yr) on RRT at death	11.0	0.3–32.3	
Median time (yr) after first transplant at death	14.4	0.0–29.7	
Cause of death			
Cardiovascular	29		30.5
Infection	29		30.5
Malignancy	12		12.6
Other	23		24.5
Unknown	2		2.1

Amstel S, Clin J Am Soc Nephrol. 2015 Dec 7; 10(12): 2198–2204.

Malignancies

Skin cancer
Nonmelanoma skin cancer
Basal cell carcinoma
Squamous cell carcinoma
Malignant melanoma

Noncutaneous cancer
Lymphoproliferative disorders
Leukemia
Fibrosarcoma
Adenocarcinoma
Brown's tumor
Grawitz tumor
Parotis carcinoma
Thyroid carcinoma
Lymphoreticular malignancy

Amstel S, Clin J Am Soc Nephrol. 2015 Dec 7; 10(12): 2198–2204.

Dialysis

CJASN Clinical Journal of American Society of Nephrology

Special Feature: Primary Care Issues for Nephrologists

Screening, Diagnosis, and Treatment of Cancer in Long-Term Dialysis Patients

Jean L. Holley

CJASN May 2007, 2 (3) 604-610; DOI: https://doi.org/10.2215/CJN.03931106

Certain cancers such as human papillomavirus–associated cervical and tongue cancer and urologic malignancies are more common among dialysis patients,

Frequencies of cancers in ESRD

Cancer	Risk Factor	Relative Risk
Renal cell	Acquired cystic disease	1.5 to 25% incidence; 3.6 to 24.1 SIR
Bladder and ureter	Balkan nephropathy analgesic abuse; oral cyclophosphamide	1.50 to 16.4 SIR
Thyroid and other endocrine organs		2.28 SIR
Cervical, uterine	HPV	2.7 to 4.3 SIR[b]
Prostate		0.93 SIR[b]; 1.8 to 2.1
Liver	Hepatitis C and B	1.4 to 4.5 SIR[b]
Tongue	HPV	1.9 SIR[b]
Multiple myeloma		4.0 SIR[b]

Holley J. CJASN May 2007, 2 (3) 604-610

Acquired Cystic Disease and Renal Cell Carcinoma in Dialysis Patients

- After 3 year on dialysis, most patients will develop acquired kidney cysts
- The incidence rises with increasing time on dialysis, and >50 to 80% of patients are affected after 10 yr.
- Acquired cystic disease is associated with a **1.6 to 7%** incidence of renal cell carcinoma

International Journal of Clinical Oncology 10 June 2019
pp 1–10 | Cite as

Elevated serum soluble interleukin-2 receptor levels increase malignancy-related risk in patients on chronic hemodialysis

Authors Authors and affiliations

Chen XiaoHong, Shen Bo, Xiang FangFang, Guo Man, Zou JianZhou, Liu ZhongHua, Lv WenLv, Cao XueSen,

China

- Patients on chronic hemodialysis have an increased incidence of malignancy due to decreased immunity.
- Soluble **interleukin-2 receptor** seemed to have an effect in the process of malignancy
- 363 patients included in this research
- During the 2-year follow-up period, malignancy events were detected in 15 (4.12%) patients.
- Levels of sIL-2R had the significantly **predictive** effect on malignancy events and **malignancy-related mortality** in the following 2 years.

Cancer incidence in patients with CKD

	Author, year [Ref] Country	Population	Sample size	Follow- up (yrs)	n observed cancers	Age* (yrs)	Sex ratio
Non end-stage CKD	Wong, 2009 [17] Australia	Population-based cohort of predominantly white Australians	3,049	10.1	711	49–97	0.74
	Jorgensen, 2008 [16] Norway	Population-based cohort of Tromso inhabitants	5,425	10.3	590	24–74	1.13
Dialysis	Vajdic, 2006 [13] Australia	ANZDATA registry Patients with ESRD studied up to 5 yrs before starting RRT	25,685	4.6	689[a]	50	1.32
	Maisonneuve, 1999 [9] Australia, New Zealand	ANZDATA registry	13,497	2.6	500	49	1.26
	Europe	ERA-EDTA registry	296,903	2.9	6,849	52	1.40
	USA	USRDS	521,404	2.2	17,695	58	1.15
	Vajdic, 2006 [13] Australia	ANZDATA registry	24,926	2.7	870[a]	54	1.31
Kidney Transplant	Adami, 2003 [11] Sweden	Transplant patients from in-patient registry	5,004	7.4	639	46	1.53
	Kasiske, 2004 [12] USA	Record linkage of USRDS with Medicare	35,765	3.0	14.9%[b]	46% > 50	1.50
	Vajdic, 2006 [13] Australia	ANZDATA registry	10,180	8.5	1,236[a]	41	1.41
	Villeneuve, 2007 [14]	CORR registry	11,033	7.3	778[a]	30% > 50	1.72

Stengel B. J Nephrol. 2010; 23(3): 253–262.

Cancer risk in patients with early stage CKD

Lung cancers
and
Urinary tract cancers

Stengel B. J Nephrol. 2010; 23(3): 253–262.

Albuminuria and cancer incidence

Jorgensen also observed a **20%** higher risk of all cancer with each standard deviation increase of albuminuria, and significant higher risks for **lung, colon, kidney, and bladder cancers.**

Jorgensen. J Am Soc Nephrol. 2008;19:992–998.

Received: 26 November 2018 | Revised: 18 March 2019 | Accepted: 8 April 2019

DOI: 10.1002/mgg3.725

Molecular Genetics & Genomic Medicine
Open Access

CLINICAL REPORT

Is polycystic kidney disease associated with malignancy in children?

Brian D. Friend[1,2] | **Kami Wolfe Schneider**[3] | **Timothy Garrington**[3] |

[1]Department of Pediatrics, UCLA Mattel Children's Hospital, Los Angeles, California

[2]Department of Pediatrics, UCSF Benioff Children's Hospital, San Francisco, California

Conclusion: Our report illustrates the potential that PKD may be associated with an increased risk for developing cancer, even in children. Further research is necessary to better understand this relationship.

Characteristics of patients with a history of PKD who developed a malignancy

TABLE 1 Characteristics of patients with a history of PKD who developed a malignancy

Patient	Age at cancer diagnosis	Gender	PKD type	PKD variant	Other genetic test results	Malignancy type
1	5 years	Male	ARPKD	*PKHD1* c.7967_7968delCA	No abnormalities identified by chromosomal microarray	Hepatocellular carcinoma
2	17 years	Male	ADPKD	*PKD1* c.1723−1G > A	No other variants identified by whole exome sequencing	Testicular germ cell tumor
3	15 years	Male	ADPKD	*PKD1* c.1723−1G > A	No other variants identified by whole exome sequencing	Testicular germ cell tumor
4	6 months	Female	ADPKD	Genetic testing not performed	Homozygous deletions of *SMARCB1* in tumor, both alleles present in blood	Renal rhabdoid tumor
5	8 years	Female	ADPKD	*PKD2* c.339delG	*TSC1*, *TSC2*, *PKD1* sequencing—no pathogenic variants detected	PEComa

ASIAN PACIFIC JOURNAL OF CANCER PREVENTION

Official publication of the Asian Pacific Organization for Cancer Prevention (APOCP)

Risk Factors for Upper and Lower Urinary Tract Cancer Death in a Japanese Population: Findings from the Japan Collaborative Cohort Study for Evaluation of Cancer Risk (JACC Study)

Article 84, Volume 17, Issue 7, July 2016, Page 3545-3549 XML

PDF (367.04 K)

Authors

Masakazu Washio; Mitsuru Mori; Kazuya Mikami; Tsuneharu Miki; Yoshiyuki Watanabe; Masahiro Nakao; Tatsuhiko Kubo; Koji Suzuki; Kotaro Ozasa; Kenji Wakai; Akiko Tamakoshi

Department of Public Health, Sapporo Medical University School of Medicine, Sapporo, Japan Email : washio@stmary.ac.jp

- Current smoking increases the risk of both upper and lower urinary tract cancer deaths
- A history of kidney disease may be a risk factor for bladder cancer death in the Japanese population.

Pediatric UTI

World Journal of Urology (2018) 36:1181–1190
https://doi.org/10.1007/s00345-018-2257-z

INVITED REVIEW

Role of urinary tract infection in bladder cancer: a systematic review and meta-analysis

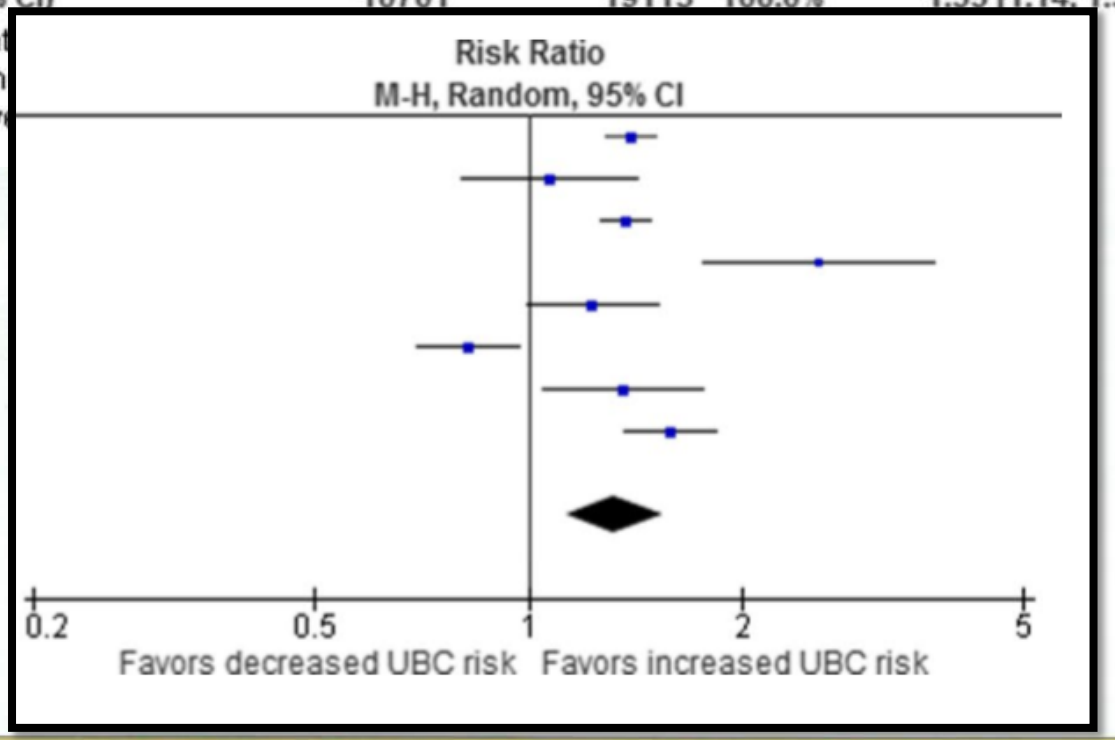
Christopher E. Bayne[1] · Dannah Farah[2] · Katherine W. Herbst[3] · Michael H. Hsieh[1,4,5]

Division of Pediatric Urology, Children's National Health System, 111 Michigan Ave, NW, Washington, DC 20010, USA

School of Medicine and Health Sciences, The George Washington University, Washington, DC, USA

Exposure to UTI favors increased risk for UBC_{NS}, particularly in men,

Study or Subgroup	Cases Events	Total	Controls Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Kantor et al (1984)	776	2932	1077	5698	15.4%	1.40 [1.29, 1.52]	1984
Kjaer et al (1989)	60	388	114	790	10.3%	1.07 [0.80, 1.43]	1989
Hartge et al (1990)	729	2806	995	5258	15.3%	1.37 [1.26, 1.49]	1990
La Vecchia et al (1991)	73	358	35	442	8.2%	2.58 [1.76, 3.76]	1991
Jhamb et al (2007)	146	652	125	689	12.3%	1.23 [1.00, 1.53]	2007
Jiang et al (2009)	221	1586	269	1586	13.6%	0.82 [0.70, 0.97]	2009
Erdurak et al (2013)	68	170	83	282	11.1%	1.36 [1.05, 1.76]	2013
Vermeulen et al (2015)	250	1809	381	4370	13.9%	1.59 [1.36, 1.84]	2015
Total (95% CI)		10701		19115	100.0%	1.33 [1.14, 1.55]	
Total event							
Heterogen							
Test for ov							



International Journal of Environmental Research and Public Health

MDPI

Int J Environ Res Public Health. 2019 Feb; 16(3): 390.
Published online 2019 Jan 30. doi: 10.3390/ijerph16030390

PMCID: PMC6388119
PMID: 30704106

Risk of Cancer after Lower Urinary Tract Infection: A Population-Based Cohort Study

Chia-Hung Huang,[1,2,†] Ying-Hsiang Chou,[1,3,4,†] Han-Wei Yeh,[5] Jing-Yang Huang,[6] Shun-Fa Yang,[1,6,*] and Chao-Bin Yeh[7,8,*] **Taiwan**

- A total of 38,084 patients with UTI and 76,168 participants without UTI were included in the control group.
- The result showed a higher hazard ratio of any cancer in both sexes with UTI
- The **genital organs, Prostate, kidney, and urinary bladder** of men were significantly more affected than those of women with prior UTI.
- Antibiotic treatment for more than 7 days associated the incidence of bladder cancer in men.

J. Clin. Med. **2019**, *8*, 819; doi:10.3390/jcm8060819

Journal of
Clinical Medicine

MDPI

Article

Effect of Statin on Cancer Incidence: An Umbrella Systematic Review and Meta-Analysis

Gwang Hun Jeong [1], Keum Hwa Lee [2,3], Jong Yeob Kim [4], Michael Eisenhut [5], Andreas Kronbichler [6], Hans J. van der Vliet [7], Sung Hwi Hong [4,8], Jae Il Shin [2,3,9,*] and Gabriele Gamerith [10]

1 College of Medicine, Gyeongsang National University, Jinju 52727, Korea; gwangh.jeong@gmail.com
2 Department of Pediatrics, Yonsei University College of Medicine, Yonsei-ro 50, Seodaemun-gu, C.P.O. Box 8044, Seoul 03722, Korea; AZSAGM@yuhs.ac
3 Division of Pediatric Nephrology, Severance Children's Hospital, Seoul 03722, Korea

a preventive effect. There was weak evidence of an association with six cancers, and no significance for the remaining eight cancers. None of the meta-analyses of RCTs on the association of statin and cancer incidence showed a statistical significance. Although there was a preventive effect of statin on cancer incidence in 10 of the 18 cancer types, the evidence supporting the use of statins to reduce cancer incidence was low. Therefore, the associations between statin use and cancer incidence should be carefully considered by clinicians.

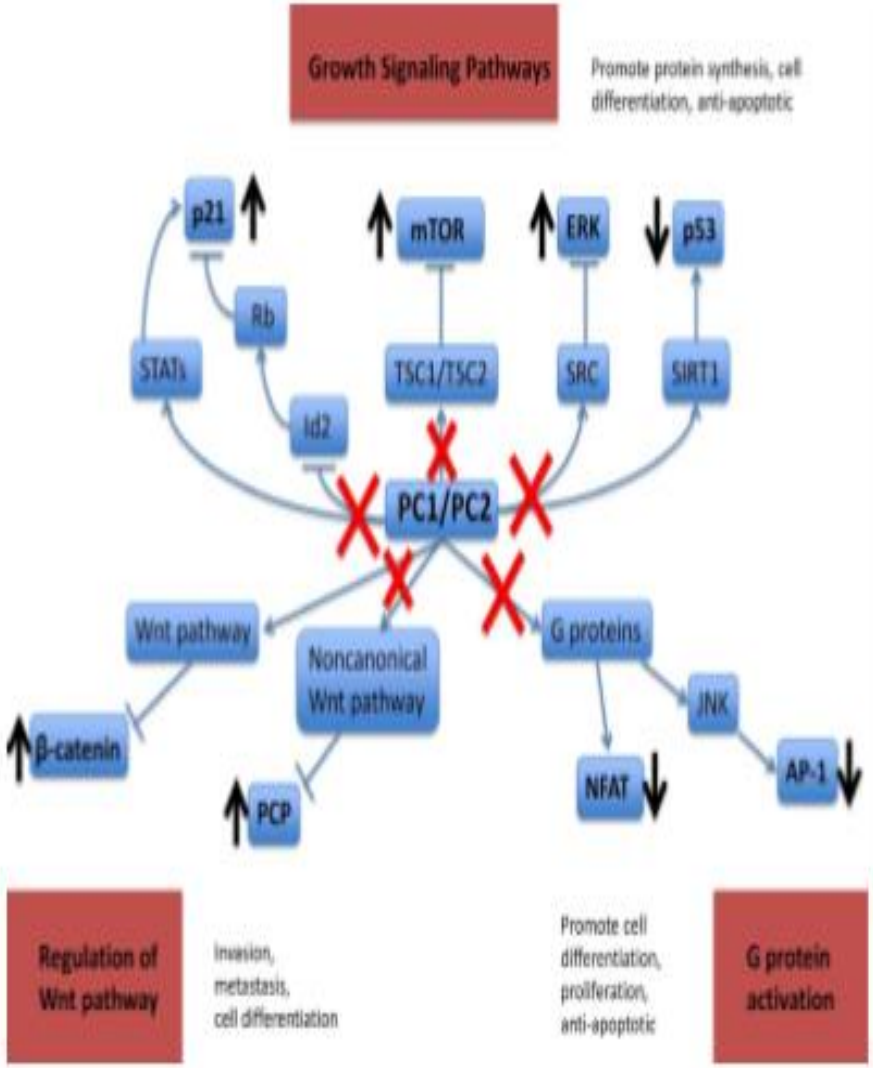


FIGURE 1 Signaling pathways present in the development of PKD that may promote oncogenesis (Chapin & Caplan, 2010; Nagao et al., 2012; Seeger-Nukpezah et al., 2015)