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Reduced kidney function associated with higher risk of renal and urothelial cancer

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Researchers who investigated the level of kidney function and subsequent cancer risk in more than one million adults have found that reduced glomerular filtration rate (GFR)—a key measure of reduced kidney function and chronic kidney disease (CKD)—is an independent risk factor for renal and urothelial cancer but not other cancer types.

The retrospective study of almost 1.2 million adult members of the Kaiser Permanente healthcare system was conducted by the Kaiser Permanente Division of Research, the University of Utah's Huntsman Cancer Institute and Memorial Sloan Kettering Cancer Center, and published online today in the *Journal of the American Society of Nephrology*.

Chronic kidney disease and cancer are both major and growing public health problems. The incidence of chronic kidney disease continues to rise, with an estimated 11.5 percent of the U.S. population having reduced glomerular filtration rate, and approximately 13.5 million Americans with stage 3 or worse chronic kidney disease.

"While multiple studies have observed higher risks of cancer in persons with end-stage renal disease, the association of less severe kidney disease with cancer remains poorly understood," said lead author William Lowrance, MD, MPH, investigator at the University of Utah's Huntsman Cancer Institute. "These findings address that knowledge gap."

Investigators studied 1,190,538 adults aged 40 years and older with

known kidney function and no history of cancer, dialysis or renal transplantation. Median follow-up of the cohort between 2000 and 2008 was 5.3 years. At their entry point to the study, patients with lower GFR were more likely to be older, be persons of color, be current or former smokers, have lower socioeconomic status, and have a higher burden of comorbidity.

During follow-up, a total of 76,809 incident cancers were documented among 72,875 subjects (38,744 men and 34,131 women). Compared with GFR (in ml/min/1.73 m2) of 60 to 89, there was an increased rate of incident renal cancer, ranging from a 39 percent increased rate for GFR of 45 to 59 to a more than two-fold increased rate for GFR less than 30. This increased rate was of greater magnitude for clear cell renal cancer as compared with non-clear cell renal cancer.

Compared with GFR of 60 to 89, researchers also found that GFR less than 30 was associated with a 48 percent increased rate of urothelial cancer. However, GFR levels below 60 were not significantly associated with prostate, colorectal, lung, breast or any cancer.

The researchers say several possible biologic mechanisms may help to explain the association between level of kidney function and renal or urothelial cancers. Kidney dysfunction results in a state of chronic inflammation and oxidative stress, and such an inflammatory microenvironment may play a role in cancer development. Severe chronic kidney disease may additionally create a relative state of immunodeficiency, which could influence the development of cancer.

"These and other mechanisms deserve further study in order to better define the link between kidney function and site-specific cancer risk," said Paul Russo, MD, FACS, study co-author and urologic surgeon at Memorial Sloan Kettering. "The stronger association of GFR and clear cell renal cancer as compared with non-clear cell provides new insights

into the biologic underpinnings of the association of chronic kidney disease and renal cancer."

As for the clinical implications of the findings, Juan Ordonez, MD, study co-author and Chair of the Chiefs of Nephrology for Kaiser Permanente Northern California, said, "If GFR is associated with an increased risk of renal and urothelial cancer, then it could have implications for directing cancer screening efforts in select populations. Currently, there are no evidence-based cancer screening recommendations tailored for patients with chronic kidney disease. Additional studies are needed to clarify the reasons for this association and help us assess the potential advantage of targeted cancer screening in patients with chronic kidney disease."

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