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See related article, "Conformational Change in Transfer RNA Is an Early Indicator of Acute Cellular Damage," on pages 2316–2326.

CKD and Risk of Renal Cell Carcinoma: A Causal Association?

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The increasing burden of CKD in the United States is an important public health concern. In addition to well established comorbidities, such as cardiovascular disease, patients with CKD may have an increased risk of renal cell carcinoma (RCC), whose incidence has also been rising in recent decades.¹ Although there is consistent evidence of an excess risk of RCC and other malignancies among patients with ESRD and kidney transplant recipients,^{2–6} few studies have investigated cancer risk in relation to less severe forms of

impaired renal function. The article by Lowrance *et al.*,⁷ published in this issue of *JASN*, reports on the relationship between eGFR and risk of RCC and several other cancers among members of the Kaiser Permanente Northern California system, a large integrated health care network in the greater San Francisco Bay area.

The well maintained records of the Kaiser Permanente Northern California system are an ideal data source for evaluating cancer risk in relation to impaired renal function, and the authors have controlled for potential confounding factors to an extent not possible in previous studies of CKD or ESRD and cancer. Others strengths of this study include its large sample size and prospective, population-based design. The investigators observed increasing risk of RCC among those with lower eGFR; this association appeared to increase monotonically, with a >2-fold risk of RCC among individuals with eGFR < 30 ml/min per 1.73 m² compared with those with eGFR of 60–89 ml/min per 1.73 m². Lower eGFR was also associated with an increased risk of urothelial (transitional cell) carcinomas, although the magnitude of this association was not as strong as that for RCC. The association with urothelial cancer is consistent with that seen in several studies reporting an increased risk of bladder cancer among patients with ESRD or those who received a transplanted kidney.^{3–6}

Although the observed association between CKD and future RCC risk may be truly causal, several alternate explanations merit consideration. One possibility is that heightened medical surveillance of individuals with impaired renal function may lead to increased incidental detection of localized, indolent renal tumors discovered through abdominal imaging. However, the authors minimized the potential effect of detection bias on their results by adjusting for health care utilization, hematuria, and receipt of medical imaging in their statistical models. Furthermore, they noted that the association between CKD and RCC was still apparent in sensitivity analyses restricted to cases with nonlocalized renal tumors who did not have abdominal imaging; we might expect that such cases would be the least likely to have their renal tumors detected incidentally.

Another possibility is that impaired kidney function may be a prodromal effect of as-yet-undiagnosed renal tumors. Lowrance *et al.*⁷ sought to account for bias resulting from reverse causation by restricting their analysis to individuals without a history of dialysis or renal transplantation before study entry, by excluding incident cancers diagnosed during the first 2 years of follow-up, and by excluding serum creatinine measurements obtained < 3 months before an incident cancer diagnosis. Although these exclusion criteria should provide some reassurance that the observed association reflects an etiologic role of CKD in renal carcinogenesis, future studies characterizing kidney function earlier in time before RCC diagnosis would further strengthen the argument against reverse causation bias. It would also be informative for future studies to characterize RCC risk in relation to the change in kidney function over time using serial measurements from specimens collected at specific time intervals before RCC diagnosis.

As the authors note, the biologic mechanisms underlying the association between CKD and RCC risk (*e.g.*, pathologic

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changes related to reduced kidney function and/or immunologic effects of CKD) also warrant further examination in future studies. Immune dysfunction among patients with renal insufficiency is well characterized,⁸ and may influence risk of both renal and urothelial cancers.⁹

Another important area of continued research following up on these findings is whether the relationship between CKD and RCC differs by race or ethnicity. The prevalence of CKD is higher, and impairment of renal function is likely to be more severe among African Americans than among non-Hispanic whites.¹⁰ Two recent studies suggest that the magnitude of the association between ESRD and RCC risk is greater among African Americans than among whites.^{11,12} Additional research is warranted to evaluate whether such racial differences in CKD might contribute to the observed excess incidence of RCC among African Americans.¹

Currently, there are no established screening protocols for kidney cancer (with the exception of those for patients with certain hereditary conditions, such as von Hippel-Lindau disease) or for bladder cancer in asymptomatic adults.^{13,14} It is possible, as noted by Lowrance *et al.*,⁷ that their findings may have implications for targeted cancer screening among some patients with CKD. However, the magnitude of the observed associations between eGFR and renal and urothelial cancers is smaller than that generally considered acceptable for screening purposes.¹⁵ As such, additional research would be needed to identify specific high-risk groups of patients with CKD and to evaluate the potential benefits and harms of screening in these populations.

In summary, this report by Lowrance *et al.*⁷ is an important step forward in characterizing the relationship between CKD and risk of RCC and other malignancies. Studies such as this further support an etiologic role of impaired renal function in the development of RCC.

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DISCLOSURES

None.

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Are Post-Trial Observational Studies Useful?

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For more than two centuries, the measurement of urinary proteins has been a standard tool for nephrologists to diagnose

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