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Editorial Comment

EDITORIAL COMMENT

The potential association between influenza vaccination and lower incidence of renal cell carcinoma

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ABSTRACT

It is well-established that kidney cancer or renal cell carcinoma (RCC) occurs more commonly in chronic kidney disease (CKD) than in the general population, although the underlying mechanisms are incompletely understood. Beyond hereditary RCC syndromes; smoking, obesity and hypertension are widely known risk factors for RCC, irrespective of CKD. Kidney-specific factors such as episodes of acute kidney injury, nephrolithiasis and cyst formation have also been shown to be associated with RCC development. One potential and less explored factor is the role of viruses in the development of kidney cancer. In this issue of *Clinical Kidney Journal*, Lin *et al*. raise the interesting hypothesis that influenza vaccination may be associated with lower incidence of RCC in adults with CKD. We discuss potential mechanisms underlying this interesting observation in the context of immune dysregulation in CKD.

Keywords: chronic kidney disease, influenza, kidney cancer, renal cell carcinoma, vaccination

In this issue of the *Clinical Kidney Journal*, Lin *et al*. report the intriguing finding that influenza vaccination in older adults with chronic kidney disease (CKD) is associated with a lower incidence of renal cell carcinoma (RCC) [1]. The retrospective propensity-matched study used an insurance claims database in Taiwan and studied 11 605 individuals over the age of 55 years with a coded diagnosis of CKD, in whom government-funded influenza vaccination is indicated. All stages of CKD were included with the exception of kidney transplant recipients and those with prior cancer, with a quarter of the cohort receiving dialysis. We review the relationship between infections, vaccination and carcinogenesis in CKD in order to contextualize the novel findings reported by Lin *et al*.

RCC represents approximately 2% of all malignancies in adults and its incidence is predicted to increase to become the fourth most commonly diagnosed cancer [2]. Patients with CKD, particularly those undergoing dialysis, are at increased risk of urogenital cancer relative to the general population [3] and men living in Western countries are especially at risk [4]. Lowrance *et al*. studied a cohort of over 1 million adults with and without CKD and found almost 2-fold increased incidence of renal and urothelial cancer at lower estimated glomerular filtration

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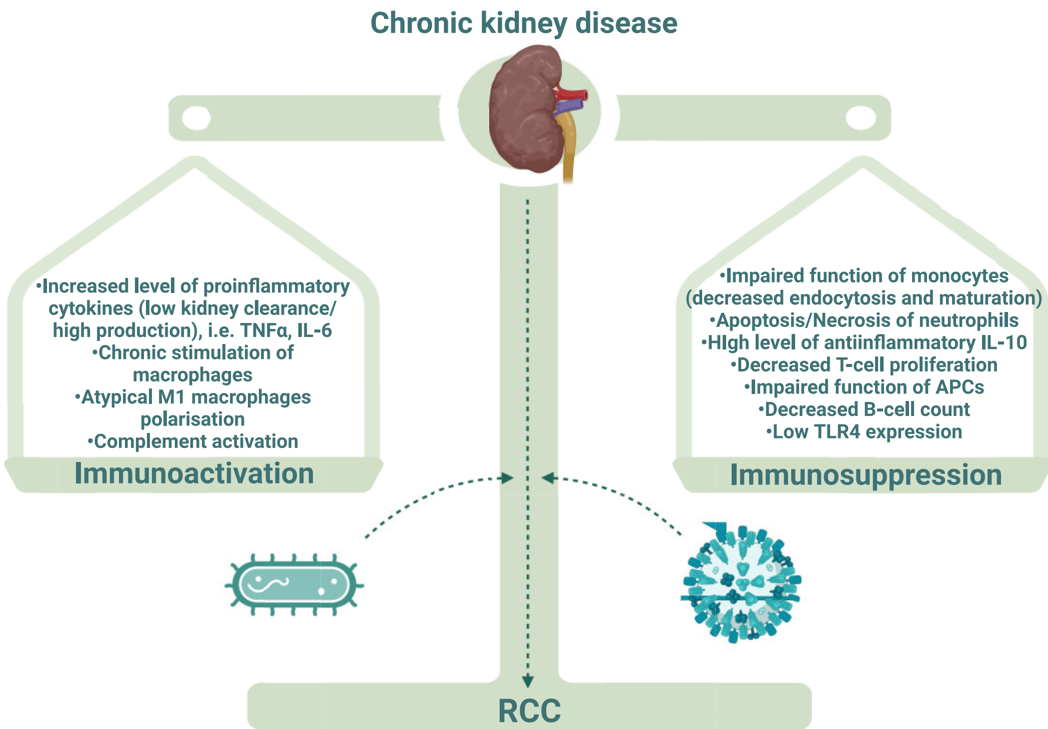

Figure 1: Inflammatory balance in CKD. Proinflammatory and immunosuppressive conditions in patients with CKD predispose to cancer formation. Infections additionally increase the cancer risk by evoking inflammatory imbalance. APC, antigen presenting cell; IL, interleukin; TLR4, toll like receptor 4; TNFα, tumor necrosis factor α. Adapted from [21]. Created with BioRender.com.

rate (eGFR; <30 versus 60–89 mL/min per 1.73 m^2); but no association with prostate, breast, lung, colorectal or total cancer incidence [5]. Miyamoto *et al.* prospectively studied a cohort of 21 978 Japanese adults with CKD and similarly found no association between eGFR and total cancer incidence, although renal or urogenital cancers were not reported specifically [6]. The mechanisms underlying the increased risk of RCC in CKD are incompletely understood and complicated by shared risk factors, such as hypertension [7]. It can be difficult to untangle this relationship to clearly attribute the increased risk of RCC in CKD patients to hypertension or to other changes in homeostasis as a consequence of kidney dysfunction. Acquired kidney cysts that can develop during the course of CKD progression also confer risk for RCC [8]. Other important risk factors for RCC include smoking, obesity and nephrolithiasis, as well as acute kidney injury (AKI) [9] and hereditary renal cell carcinoma syndromes [7]. Although infection and cardiovascular disease are the most common causes of death in CKD, cancer contributes significantly to morbidity and mortality. Outcomes are poor, in part due to late diagnosis and limited therapeutic options, therefore there is need for improved understanding of cancer pathogenesis, specifically of RCC in those with pre-existing CKD. Screening is not recommended across the CKD population but attention should be paid in patients at particularly increased risk [3], for example kidney transplant recipients in whom immunosuppression contributes to increased risk [10]. Diagnosis of RCC relies upon imaging techniques and technological advances have resulted in earlier diagnosis [11]. Earlier diagnosis has undoubtedly contributed to improved survival but there remains significant morbidity following successful treatment, and nephrectomized patients require close follow-up to monitor kidney function and manage comorbidities [7].

Infections may also play a role and viruses specifically have established carcinogenic effects. Although upto 10–20% of cancers are known to be associated with viral infections [12], the role of viruses in carcinogenesis is not fully understood. The Epstein–Barr virus causes lymphoproliferative disease, for example, and the human papilloma virus is a recognized cause of cervical cancer which can be effectively prevented by vaccination [13]. Less is known about the influenza virus and cancer, although a recent study by Garmendia *et al.* showed that acute influenza infection modified tumour microenvironment and impaired T cell responses, leading to tumour growth in an animal model of lung cancer [14]. What is more, Chen *et al.* reported significantly lower risk of lung cancer in influenza vaccination recipients with CKD [15]. An interesting observation was made by Shih *et al.*, who observed significantly lower risk of AKI after influenza vaccination [16]. In this manner, reduction of AKI after influenza vaccination may lower RCC risk, since AKI itself is known to predispose to RCC [9]. The exploration of the association between influenza vaccination and RCC specifically is relatively novel. Lin *et al.* report an eye-catching estimate of 54% lower hazards for incident RCC in individuals vaccinated against influenza versus those who are unvaccinated [adjusted hazard ratio (HR) 0.46, 95% confidence interval (CI) 0.28–0.75] [1]. What is especially intriguing is that Lin *et al.* reported that this protective effect was predominant in older adults, in whom vaccine efficacy is known to be lower [17, 18], which might have led us to anticipate attenuated or absent effects in the older study participants. The authors report large effects in those aged 75 years and over (HR 0.22, 95% CI 0.08–0.58) but apparently no significant effect in those aged 55–74 years (HR 0.59, 95% CI 0.32–1.09) who constitute more than two-thirds of the study cohort; however, a statistical test for interaction between vaccination and age is not reported. Response

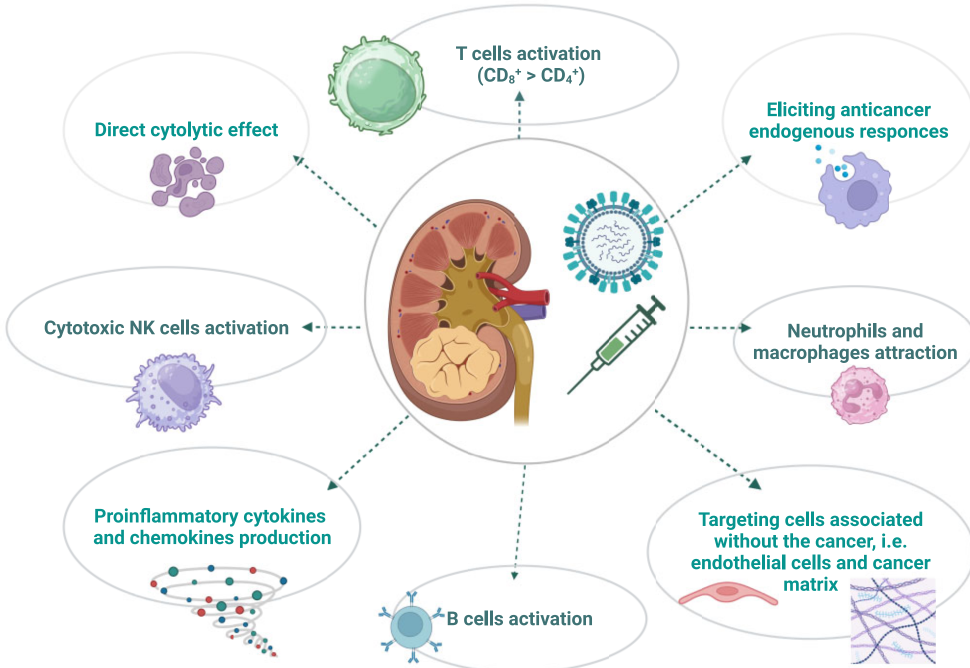

Figure 2: Proposed mechanisms of antiviral vaccine effects on cancer cells. Adapted from [24]. Created with BioRender.com.

to vaccination is also markedly attenuated at lower levels of kidney function and reportedly non-existent in dialysis patients [19, 20]. The authors can be commended for including large numbers of patients receiving dialysis in the study since this group are often excluded and understudied. Lin *et al.* report consistently protective effects of influenza vaccination and RCC incidence irrespective of dialysis status.

It is well established that abnormalities in the adaptive immune system are responsible for higher risk of infections in CKD patients (Fig. 1) [21]. Since infections remain the second most common cause of death in people with CKD [22], and comorbid CKD increases infection-related morbidity and mortality, vaccination is prioritized in this cohort. Impaired T-cell maturation and activation in particular are claimed to be responsible for non-response to vaccination, i.e. against hepatitis B, influenza, *Clostridium tetani*, tuberculosis or COVID-19 in patients with impaired kidney function [19, 23]. Other aspects of immune system activation may also play a role in potential anticancer effects of vaccines. In particular the activation of cytotoxic T cells, together with natural killer cells and macrophage stimulation, and the modification of extracellular matrix are mechanisms that may underlie anticancer effects of vaccines, used already in the targeted treatment of cancers (Fig. 2) [24]. It can be speculated that the influenza vaccine protects against cancer, especially in older people with CKD with already impaired immune system activity, with a greater propensity for mutagenesis and cancer formation, although the precise mechanism is incompletely understood. Consideration of potential explanatory mechanisms underlying Lin *et al.*'s findings is purely speculative since occurrence and severity of influenza infection, in association with vaccination patterns and RCC incidence, is not reported. The purported reduction in RCC risk may plausibly be explained by lower incidence and severity of influenza infection and related complications or alternatively, direct anti-cancer effects of vaccination may be at play; however, the study by Lin *et al.* is unable to answer such questions. Furthermore, the study was not able to assess with reasonable certainty any dose-dependent association between frequency of vaccination and RCC incidence.

The strengths of the novel study lie in its large cohort with propensity score matching though several key limitations preclude conclusive findings. Unmeasured confounding may be responsible for biased effect estimates and the observational nature of the study precludes causal inference. Exposure to smoking and other carcinogenic pollutants were not available which is a key limitation given the causative role of tobacco smoking in RCC and its likely differential associations with vaccination behaviours. No assessment was made of CKD severity and those with earlier stage CKD may be underrepresented since eligibility depended upon coded diagnoses of CKD which may bias inclusion towards more severe CKD patients, in whom the risk of RCC is inherently greater. Considering these limitations, the results can be regarded as hypothesis-generating at best though they do support the already established public health policy of influenza vaccination in CKD. The authors' findings raise an interesting hypothesis worthy of further investigation to elucidate the potential mechanisms underlying the observed association between influenza vaccination and cancer in CKD.

CONFLICT OF INTEREST STATEMENT

K.J.M. has no personal disclosures but reports grant funding paid to her institution (CTSU, NDPH, University of Oxford) from Boehringer Ingelheim and Eli Lilly. B.M.S. and I.Z. have no conflicts to disclose.

(See related article by Lin et al. Influenza vaccination is associated with lower risk of renal cell carcinoma among chronic kidney disease patients: a population-based cohort study. *Clin Kidney J* (2023) 16: 1936–1946.)

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