Lifetime Risk of CKD: What Does It Really Mean?

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Life is inherently risky. Some individuals manage to avoid the consequences of these risks over many years, whereas others are not so fortunate. The lifetime risk of dying, of course, is 100%. However, the magnitude of the risk for acquiring a diagnosis of a specific disease or group of diseases over a lifetime (also called cumulative incidence of diseases) varies widely according to the frequency of the disease in the population as a whole, how the occurrence of the disease is spread over the lifetime of individuals, and how the disease is defined and ascertained. For example, the lifetime risk of developing cancer is 1 in 2; however, the lifetime risk for colon cancer specifically is 1 in 21. Diseases are often defined as a departure from a reference population of normal, healthy persons; however, making such a clear separation between disease and normality is often a difficult task (1). This is especially true in the case of identifying generic CKD, because clinical manifestations often occur late and frequently not even until RRT is needed (2,3). Thus, nephrologists have come to rely heavily on biomarkers, mainly eGFR and albuminuria (or proteinuria), for definition of generic CKD (2). Although measured GFR (mGFR; by inulin, iohexol, or iothalamate clearances) is the preferred method of assessing GFR when a high degree of precision is required in a given individual or in clinical trials, an eGFR using an equation based on serum creatinine or serum cystatin C concentrations or their combination is sufficient for many clinical and nearly all epidemiologic purposes (4,5). Albuminuria (or proteinuria) can be determined by qualitative or quantitative tests on untimed or timed urine samples. Applying the results of these biomarker assessments for diagnosing CKD and thus determining risk over time is a daunting task with numerous challenges.

The issue of diagnosing CKD is central to understanding results of a study of lifetime risk of developing stage 3–5 CKD in a well characterized Icelandic population of men and women reported by Inker *et al.* in this issue of *CJASN* (6). The authors prospectively followed for 25 years (from 1967 to 2005) 3888 people in Iceland. At baseline, the mean age was 47±7 years, both genders were equally represented, and all participants had an eGFR (calculated by the Chronic Kidney Disease Epidemiology Collaboration equation) >60 ml/min per 1.73 m^2. Such a long follow-up in a large sample of patients is quite unique in the nephrologic literature. The goal of the authors was to assess the lifetime risk (cumulative incidence) of generic CKD defined as (*1*) an eGFR of <60 ml/min per 1.73 m^2 on two consecutive measurements [equal to that utilized by the Kidney Disease Improving Global Outcomes clinical practice guidelines (2)], (*2*) kidney failure treated by dialysis or transplantation, (*3*) one measurement of eGFR <45 ml/min per 1.73 m^2 if it was the last measurement, or (*4*) one measurement of eGFR <60 ml/min per 1.73 m^2 if the patient died before the next measurement. Albuminuria (or proteinuria) was not assessed. Obviously, the lifetime risk of generic CKD was very dependent on the definition used for CKD. For example, the risk of CKD at 20 years for a 45-year-old woman was 8.6% if CKD was defined by two consecutive measurements of eGFR<60 ml/min per 1.73 m^2 or 16.8% if CKD was defined by only one measurement of eGFR <60 ml/min per 1.73 m^2 (6). Because chronicity implies a notion of time by its nature, the first CKD definition (with a second confirmatory result) seems more relevant (2). In addition, the specific threshold of eGFR used in this analysis for separating CKD from non-CKD is arbitrary and absolute, rather than stratified by age.

These results need to be contrasted with other studies that examined lifetime risk of CKD, including retrospective, simulation models in which CKD was defined by only one value of eGFR (7,8). In their longitudinal analysis, Inker *et al.* clearly demonstrated that eGFR decreased progressively with aging; unsurprisingly, the diagnosis of CKD, using a single threshold, increased with aging (6). Unfortunately, the absence of data on eGFR slopes with aging makes it difficult to compare this study with other longitudinal studies on the decline of GFR with aging (9,10). In the context of the well established GFR decline with healthy aging, the reference base of normality is also very important. Cross-sectional data with eGFR and mGFR have clearly shown that otherwise healthy people demonstrate a decline in GFR to values <60 ml/min per 1.73 m^2 with aging, especially in women aged >65 years (3,11–14). Thus, it is not surprising that using the definitions of Inker *et al.*, the lifetime risk (to age 85 years) of CKD is greater in women than in men; this is the opposite of what is seen from calculations of lifetime risk of treated ESRD, in which men have a greater (about 1.5-fold) risk than women (15). Although many alternative schemas for defining CKD based on eGFR are possible, one that alters the threshold based on age is both plausible and desirable (16). For example, we have proposed that an isolated GFR <45 ml/min per 1.73 m^2 (CKD stage 3B)

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should become the new eGFR threshold for definition of CKD in people aged >65 years without any albuminuria or other signs of kidney damage (16). A change in the criteria for defining CKD would have a substantial effect on the cumulative incidence of CKD in the population at large. Indeed, applying an age-stratified eGFR threshold to the data of Inker *et al.* (Table 4 in their study), one finds that the lifetime risk of reaching stage 3 CKD after 20 years of follow-up of a 55-year-old person decreases from 15.2% to 3.1% in men and from 30.4% to 4.4% in women (6). Because albuminuria results are not available in this analysis, the true CKD prevalence cannot be calculated; however, we know that the vast majority of CKD in people aged >65 years is diagnosed only according to the eGFR threshold criteria (17).

The data of Inker *et al.* are purely descriptive and thus cannot specifically address the long-lasting but still unresolved debate between opponents and defenders of an "age-calibrated" eGFR or other alternative schemas for definition of generic CKD (16,18). However, the observed association between decreased eGFR (*i.e.*, <60 ml/min per 1.73 m^2) and mortality (all-cause or cardiovascular) is an important justification for the choice of the GFR threshold for CKD definition. One study showed that association between eGFR and mortality or ESRD <60 ml/min per 1.73 m^2 was similar in young and elderly people (19). However, the calculation of hazard ratios is subject to several alternative interpretations (20). In addition, data from a large Canadian database confirmed that life expectancy was similar in elderly persons if stage 3A CKD or stage 1–2 CKD were compared (21). In a very recent study from Sweden, eGFR was followed in elderly women for 10 years between ages 75 and 85 years. This study also found that stage 3B CKD, but not stage 3A, was associated with mortality in 1011 women considered at baseline; however, large confidence intervals and a potential lack of statistical power do not fully exclude a clinically important higher risk even in stage 3A (22).

It must also be emphasized that no evidence currently exists to show that treating patients aged >65 years with stage 3A CKD without albuminuria or other signs of CKD is useful, cost-effective, or even safe. Indeed, renin-angiotensin system (RAS) inhibitors are undoubtedly the most effective therapies in nephrology to prevent ESRD. However, a recent simulation study with real-life data demonstrated that therapies with RAS inhibition would be considered totally ineffective if studies were performed in elderly patients with stage 3A CKD and no albuminuria (23). Our interpretation is that these elderly individuals with decreased GFR are actually not CKD patients. In this context, it must be underlined that the unique and absolute threshold of 60 ml/min per 1.73 m^2 for eGFR-based CKD classification is also questionable in young people, especially if data on albuminuria are lacking. A patient aged 20 years with an eGFR of 65 ml/min per 1.73 m^2 is certainly a candidate for CKD diagnosis and will have a high lifetime risk of later stages of CKD and of treated ESRD (24). These young people, often with very specific nephrologic diseases like GN, are much less common than elderly patients with CKD; however, there is a need to also focus on this group because interventions to prevent progression may be more effective. In addition, one cannot extrapolate the results of Inker *et al.* to other ancestral populations such as African Americans or Asians.

In conclusion, the data and analysis of Inker *et al.* are novel and of great interest, particularly because studies of such long duration are few and far between. This study is also a good illustration of the effect of a given arbitrary definition on the epidemiology of CKD. Every definition using cutoffs or thresholds (including an age-calibrated definition) is an arbitrary choice at worst or a fair trade-off at best. This is especially the case for GFR, which physiologically declines with aging. The best scientific tool to define normality for such a "moving" parameter would be the use of percentiles, like pediatricians use every day for height and weight. Using such normograms available in the literature (11–14) would avoid both false negative (in young people) and false positive (in elderly individuals) diagnoses of CKD. Because this strategy might be considered too complex or cumbersome for daily practice, the use of a specific threshold is favored; however, an age-calibrated threshold seems like good trade-off that is balanced between the two extremes (percentiles on one side and a unique threshold on the other side). In summary, we suggest that the lifetime risk of CKD is much less than Inker *et al.* allege, largely because the definitions of CKD utilized by Inker *et al.* can be challenged even though they substantially conform to existing guidelines (2). The lack of an age calibration of eGFR thresholds for defining CKD plausibly results in an inflation of the cumulative incidence of CKD as populations and individuals age, more so in women than in men.

Disclosures

None.

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