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Epidemiology of the Small Renal Mass and the Treatment Disconnect Phenomenon

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Synopsis

The incidence of kidney cancer has steadily increased over recent decades, with the majority of new cases now found when lesions are asymptomatic and small. This downward stage migration, in part, relates to the increasing use of abdominal imaging. Three public health epidemics—smoking, hypertension, and obesity—also play a role in the increasing incidence of the disease. Treatment of kidney cancer has mirrored the rise in incidence, with increasing interest in nephron-sparing therapies. Despite earlier detection and increasing treatment, the mortality rate of kidney cancer has not decreased. This treatment disconnect phenomenon highlights the need to decrease unnecessary treatment of indolent tumors and address modifiable risk factors, which may ultimately reduce kidney cancer incidence and mortality.

Keywords

Kidney Cancer; Epidemiology; Incidence; Mortality; Treatment Disconnect

Introduction

The epidemiology of kidney cancer has evolved in recent decades in response to the changing clinical presentation of the disease. Although historically associated with symptoms at presentation, fewer than 10% of renal cancers today present with the classic triad of hematuria, pain, and a palpable mass.¹ Most renal masses are now “screen-detected” as small, asymptomatic, incidental findings on imaging studies performed for unrelated reasons. As a consequence of the increased adoption of cross-sectional imaging, the incidence of renal cancer has increased, and there has been a stage migration towards earlier stage tumors. The rising incidence of kidney cancer is also thought to be, in part, due to the

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rising prevalence of associated risk factors and three public health epidemics: smoking, hypertension, and obesity.

While early detection and treatment of early stage kidney cancer should theoretically result in improved survival outcomes, there has been an apparent rise in mortality rates over the past 20 years.^{2,3} This paradox has held true even after accounting for stage and size migration. Termed “treatment disconnect,” this phenomenon has impacted contemporary management and policy perspectives related to kidney cancer. This article reviews the changing epidemiology of kidney cancer, public health epidemics associated with its rising incidence, potential explanations for the treatment disconnect phenomenon, and their implications on public policy.

Risk Factors

Smoking

Tobacco smoke is the most common human carcinogen and is noted to be the predominant risk factor in 20–25% of renal cell carcinoma cases.⁴ It is estimated that there were more than one billion smokers worldwide in 2015.⁵ In a recent meta-analysis of 109 case-control studies and 37 cohort studies, the risk of developing renal cell carcinoma was higher for current smokers (relative risk [RR] 1.36, 95% confidence interval [CI] 1.19–1.56) and former smokers (RR 1.16, 95% CI 1.08–1.25) compared with nonsmokers.⁶ The association between smoking and kidney cancer appears to be slightly greater in men than woman, and there appears to be a dose dose-related effect, with greater risk noted in those who smoke more than 20 cigarettes per day compared with fewer than 10 per day.⁷ The role of second-hand smoke exposure is unknown.⁶

Importantly, smoking cessation may mitigate the risk of kidney cancer.⁷ In a population-based case-control study in Iowa, there was an inverse linear relationship between the risk of renal cell carcinoma and the number of years after cessation of smoking.⁸ Additionally, those with a distant (30 or more years prior) tobacco history experienced a 50% reduction in risk compared with current smokers (OR 0.5, 95% CI 0.4–0.8).

Hypertension

Hypertension is another well-known and potentially modifiable risk factor for the development of kidney cancer. A recent longitudinal study of 156,774 women enrolled in the Women’s Health Initiative (WHI) observational study and clinical trial demonstrated an excess risk of kidney cancer with increasing systolic blood pressure levels, a relationship that persisted after adjustment for age, smoking, race, and body mass index (Table 1).⁹ An elevated diastolic blood pressure (≥ 90 mm Hg) was also independently associated with kidney cancer. Similar relationships have been observed in men as well.^{10,11} Furthermore, the duration of hypertension appears to be closely associated with development of kidney cancer.¹² Although some evidence suggests that controlling blood pressure can help lower renal cancer risk, the role of hypertensive drug therapy in reducing this risk is unclear.^{13,14}

Hypertension is more prevalent among blacks than whites and is thought to play a role in the racial disparity of renal cancer incidence. Data from the National Health and Nutrition

Examination Survey (NHANES) between 1999–2004 showed age-adjusted prevalences of 39% and 28% for black and white men, respectively, and 41% and 27% for black and white women, respectively.¹⁵ In an updated analysis of data through 2012, the prevalence of hypertension remained greater in blacks than whites (odds ratio [OR] 1.86, 95% CI 1.64–2.12).

The association between hypertension and kidney cancer also appears to be stronger in blacks than whites. In a population-based case-control study from 2002–2007, renal cancer risk increased with increasing time since the diagnosis of hypertension, with a greater effect in blacks.¹³ A similar pattern was observed for decreasing levels of blood pressure control, with worse control associated with increased cancer risk. When both race and sex were considered, black women had the strongest association of hypertension with renal cancer.

Obesity

Multiple studies have demonstrated an association between obesity and kidney cancer, which is particularly notable given the continued rise in prevalence of obesity in the United States over the past decade.¹⁶ In 2011–2014, more than one in three adults were obese.¹⁶ In data from the Women's Health Initiative (WHI) observational study and clinical trial⁹, both increasing body mass index (BMI) and waist circumference were associated with kidney cancer. In the adjusted analyses, the risk of kidney cancer was over 2-fold higher in those women with a BMI ≥ 40 compared to those women with a BMI < 25 (hazard ratio [HR] 2.30, 95% CI 1.15–2.28, Table 1).

Obesity and hypertension, to some extent, may represent a shared causal mechanism in the development of kidney cancer.⁹ Obesity is a risk factor for hypertension, and both have been associated with oxidative stress and lipid peroxidation, which are thought to have a role in oncogenesis.^{17,18} One prospective study identified a relative risk of 2.82 (95% CI 1.97–4.02) for kidney cancer in patients who were both hypertensive and obese compared with those who were neither.¹⁹

Rising Incidence

In contrast to the stable or declining trends for most cancers, the incidence rates of kidney cancer have increased over the past four decades. In the United States from 1983 to 2002, the overall incidence of kidney cancer rose from 7.1 to 10.8 per 100,000 population, an increase of 52%.² The incidence has continued to rise (Figure 1A), and more than 62,000 men and women will be diagnosed with kidney cancer in the 2016.^{20–22} In an age-adjusted analysis, new cases of kidney cancer rose by an annual 1.1% from 2004 to 2013³. The incidence rates have increased for men and women of every race/ethnicity (except American Indian or Alaska native men) and have increased for every age group.²³ Similar trends have been noted in Canada, where cases have nearly doubled since 1970.²⁴ European registries have also noted a similar rise in incidence rates, though there is significant regional geographic variation in trends.²⁵

This rise in incidence is primarily due to the rise in the detection of small, asymptomatic renal tumors following the rapid adoption of cross-sectional abdominal imaging. As a

consequence, there has been a downward stage migration (Figure 1B). In an analysis of Surveillance Epidemiology and End Results (SEER) cancer registry data, the estimated age-adjusted incidence rate of localized stage tumors increased from 7.6 per 100,000 population in 1999 to 12.2 per 100,000 population in 2008, a trend not present among regional or distant stage cancers.²³ Additionally, data from the National Cancer Data Base (NCDB) demonstrated that Stage I renal cell carcinoma increased from approximately 43% to 57% of new diagnoses between 1993 and 2004.²⁶ In that study, there was a concomitant decrease in the proportion of all other stages of disease during the same time interval. Further, among those patients with stage T1a kidney cancers (less than 4 cm), tumor size at presentation decreased over time.²⁷ Although subject to bias, single-institutional series have also demonstrated an increase in the proportion of patients who presented with early stage disease over this time period.^{1,28,29}

Earlier detection of small renal masses due to abdominal imaging is unlikely to be the sole reason for the rising incidence of kidney cancer, however. Widespread implementation of screening tests (e.g. cross-sectional imaging) typically produces an initial increase in the incidence of the screened disease, as previously unsuspected tumors in the preclinical phase are identified.³⁰ As the available reservoir of patients becomes depleted, however, the incidence will correspondingly fall. Furthermore, given that most tumors will now be identified at an earlier stage, a proportionally smaller number of cases will be diagnosed at more advanced stages. For example, the incidence of prostate cancer sharply rose after the prostate-specific antigen test was introduced in the late 1980s, but started to decline after 1992, with the sharpest declines in the incidence of metastatic disease. A similar pattern has not been seen in kidney cancer, where the incidence continues to rise two decades following the adoption of cross-sectional imaging. Moreover, there has not been a concomitant reduction in the incidence of regional or distant disease.

Treatment Epidemiology

The rising incidence of kidney cancer has resulted in a similar increase in surgical intervention. For decades, the treatment paradigm for renal cell carcinoma favored expedient removal upon detection. This has been based on the assumption that early intervention (i.e. treatment of low stage disease) will achieve better long-term survival outcomes. As expected, from 1983 to 2002, trends in renal surgery mirrored the annual incidence of kidney cancer.²

The downward stage migration and small size of renal tumors at the time of diagnosis generated interest and experience with nephron-sparing surgery. As a result, the use of partial nephrectomy has increased; even still, it was not until 2009 that partial nephrectomy became the predominant treatment for patients with early-stage kidney cancer, largely due to the technical challenges of the procedure.^{31–34} That year, guidelines released by the American Urological Association emphasized the continued underuse of minimally-invasive or open partial nephrectomy, trading the long-term benefit of sustained renal function for the short-term benefit of a potentially more expedient recovery with laparoscopic radical nephrectomy.³⁵

Over the past two decades, in situ ablation of small renal masses has also been introduced as a therapeutic option.^{36,37} Using either radiofrequency ablation or cryoablation equipment, this procedure can be performed either laparoscopically or percutaneously. Use of ablation therapy continues to increase.³¹ Although this approach lacks long-term efficacy data, it is an attractive alternative option for ill or elderly patients deemed poor risk for general anesthesia and surgical resection. In an analysis of SEER data, seniors aged 65 to 74, 75 to 84, and 85 years had a 1.5-, 2.2-, and 2.0- fold greater probability of undergoing ablation compared with surgical management.³¹

Rising Mortality and Treatment Disconnect

Over the past three decades, population-based SEER data have demonstrated an improvement in the 5-year survival for kidney cancer. The 5-year relative survival increased from 50.1% between 1975–1977 to 74.7% between 2006–2012.³ Similarly, 5-year survival rates for localized disease increased from 88.4% between 1992–1995 to 92.5% between 2006–2012.²³

However, these apparent survival gains are not necessarily related to true improvements in mortality or effectiveness of cancer care (Table 2).³⁸ Any advance in the time of diagnosis—a recent phenomenon with kidney cancer—will appear to increase 5-year survival because of the spurious effect of lead time. If early treatment is effective, patients will live longer and mortality rates will improve. If early treatment is ineffective, however, patients will die at the age they would have died if their cancer had not been detected, resulting in no true improvement in mortality.

On the other hand, increases in incidence due to a true rise in occurrence (as opposed to a rise due to earlier detection) result in no changes in survival rates. To account for the complex relationship between incidence and mortality rates, some have advocated for consideration of mortality rates normalized by the change in the incidence rate (mortality over incidence, [MOI]).^{39,40} While this approach mitigates the effect of early diagnosis on survival rates, it does properly capture improved survival times in cases when mortality rates do not change.³⁹

Unfortunately, in the case of kidney cancer, improved 5-year survival rates have not translated to improvements in mortality rates. Despite an increase in early detection and treatment, the mortality rates for kidney cancer rose over the past three decades. From 1983 to 2002, kidney cancer-specific and overall mortality rates rose from 1.2 to 3.2 deaths per 100,000 U.S. population and from 1.5 to 6.5 deaths per 100,000 U.S. population, representing a 155% and 323% increase, respectively.² In an updated analysis of 2009–2013 data, the age-adjusted cancer death rate rose further to 3.9 per 100,000 U.S. population.³ However, a recent study suggests that missing tumor size data may have led to overestimates in the adjusted mortality rates reported in large population-based series.⁴¹ Imputation of tumor size appears to substantially diminish the adjusted mortality rates and may explain much of the treatment disconnect phenomenon (Figure 2). The authors considered the effect of rising incidence by adjusting for the cumulative incidence rate. They also examined the MOI ratio as another metric for investigating the relationship between mortality and

incidence. Both analyses further supported their findings that the rise in kidney cancer mortality is likely smaller than previously described, and its precise quantification is markedly confounded by the rising incidence of the disease.⁴¹

Treatment and Policy Implications

The treatment disconnect phenomenon in kidney cancer suggests that many incidentally discovered small renal masses are of indolent nature and do not require treatment. In response, enthusiasm for active surveillance of small renal masses has increased, particularly in older patients with significant comorbidity and shorter life expectancy.⁴² Using an algorithm that combines renal mass biopsy pathology and size may also decrease the treatment of indolent tumors.⁴³ With growing interest in cost savings and value-based care, changing reimbursement structures (i.e. bundled payment models) may continue to evolve and target the overtreatment of small renal masses.

Public policies that aim to reduce the three modifiable risks factors of kidney cancer—smoking, hypertension, and obesity—may ultimately impact mortality rates of the disease. Given the profound effects of tobacco use on malignancy and overall health, the Affordable Care Act mandates that all private insurers cover smoking cessation with premium reductions for smokers who enroll in a cessation program.⁴⁴ *Healthy People*, an initiative launched by the Department of Health and Human Services in 1979, provides evidence-based 10-year national objectives to promote public health.⁴⁵ Part of this program, calls for more comprehensive state Medicare coverage of smoking cessation programs, which has led to increased quit rates.⁴⁶ *Healthy People 2020*, the current plan, established goals for decreasing hypertension prevalence as well as improving treatment rates and blood pressure control.⁴⁷ *Let's Move*, a public health campaign, aims to reduce the prevalence of obesity by revamping the nutritional labeling of products by the U.S. Department of Agriculture (USDA), improving the nutritional standards of the National School Lunch Program, increasing children's opportunities for physical activity, and improving access to high-quality foods in all U.S. Communities.⁴⁸ There is hope that these public health efforts will help reduce the burden of several diseases, including kidney cancer.

Summary

The incidence of kidney cancer has steadily increased over recent decades, with the majority of new cases now found when lesions are asymptomatic and small. This downward stage migration has, in part, been related to the increasing use of cross-sectional abdominal imaging. Three public health epidemics—smoking, hypertension, and obesity—also play a role in the increasing incidence of the disease. Treatment of kidney cancer has mirrored the rise in incidence, with increasing utilization of nephron-sparing therapies. Despite earlier detection and increasing treatment, kidney cancer mortality has not decreased. This treatment disconnect phenomenon highlights the need to decrease unnecessary treatment of indolent tumors and address modifiable risk factors, which may ultimately reduce both incidence and mortality.

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Key Points

- The incidence of kidney cancer has steadily increased over recent decades, with the majority of new cases found when asymptomatic and small
- Smoking, hypertension, and obesity are associated with an increased risk of kidney cancer
- Despite earlier detection and increasing treatment, the mortality rate of kidney cancer has not decreased
- The “treatment disconnect” phenomenon in kidney cancer highlights a need to reduce overtreatment of small, indolent tumors

Figure 1.

Overall age-adjusted incidence rates of kidney cancer [A] and stratified according to disease stage [B], Surveillance, Epidemiology, and End Results, 1975–2009.

From Gandaglia G, Ravi P, Abdollah F, et al. Contemporary incidence and mortality rates of kidney cancer in the United States. *Canadian Urological Association Journal* 2014;8(7–8): 247–52; with permission.

Figure 2.

Age-adjusted [A] overall and [B] kidney cancer-specific mortality (# of deaths per 100,000) by tumor size shows attenuation of mortality rates when accounting for missing data [C and D].

From Smaldone MC, Egleston B, Hollingsworth JM, et al. Understanding treatment disconnect and mortality trends in renal cell carcinoma using tumor registry data. *Med Care* 2016 [Epub ahead of print]; with permission.

Table 1

Cox Regression of Kidney Cancer Incidence with a Model Combining Body Mass Index and Blood Pressure in the Women's Health Initiative Studies

Variables	Hazard Ratio (95% CI)
Age	1.03 (1.01–1.04)
Body mass index (kg/m²)	
18.5–24.9	reference
25–29.9	1.28 (1–1.65)
30–34.9	1.39 (1.04–1.86)
35–39.9	1.79 (1.24–2.58)
40 or more	2.30 (1.49–3.54)
Smoking	
No	reference
Yes	1.62 (1.15–2.28)
Systolic blood pressure (mmHg)	
120.0 or less	reference
120.1–130.0	1.33 (1.01–1.75)
130.1–140.0	1.24 (0.92–1.67)
140.1–150.0	1.93 (1.42–2.63)
150.1–160.0	1.48 (0.97–2.26)
160.0 or more	1.54 (0.96–2.25)
Diabetes	
No	reference
Yes	0.97 (0.65–1.45)

Multivariable model adjusted for age, race/ethnicity, body mass index, smoking, systolic blood pressure, and diabetes. CI denotes confidence interval.

Data from Sanfilippo KM, McTigue KM, Fidler CJ, et al. Hypertension and obesity and the risk of kidney cancer in 2 large cohorts of US men and women. *Hypertension* 2014;63(5):934–41.

Table 2

Relationships between Changes in 5-Year Survival, Mortality, and Incidence Under Various Conditions *

Condition	Expected Change in		
	5-year Survival	Mortality	Incidence
<i>More effective treatment of existing disease</i>	↑	↓	No change
<i>More cases found early and... early treatment is effective</i>	↑	↓	↑
early treatment is ineffective	↑	No change **	↑
<i>Increase in the true occurrence of disease without change in tumor aggressiveness</i>	No change	↑	↑

* Expected changes assume only 1 condition occurs at a given time.

** If the enhanced ability to find cancer leads to cancer being more frequently coded as the primary cause of death, mortality may even increase.

Adapted from Welch HG, Schwartz LM, Woloshin S. Are increasing 5-year survival rates evidence of success against cancer? JAMA 2000;283(22):2975–8; with permission.