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Urinary Biomarkers for the Early Diagnosis of Kidney Cancer

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See "Screening for Kidney Cancer: Is There a Role for Aquaporin-1 and Adipophilin?" on page 410.

Abstract

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OBJECTIVE: To test the hypothesis that increased tumor expression of proteins such as aquaporin-1 (AQP1) and adipophilin (ADFP) in patients with renal cancer would result in increased urine AQP1 and ADFP excretion.

PATIENTS AND METHODS: Prenephrectomy and postnephrectomy (pseudocontrol) urine samples were collected from 42 patients with an incidental radiographically discovered renal mass and presurgical presumptive diagnosis of kidney cancer from July 8, 2008, through March 10, 2009. Also enrolled were 15 control patients who underwent nonrenal surgery and 19 healthy volunteers. Urine AQP1 and ADFP concentrations normalized to urine creatinine were determined by sensitive and specific Western blot assays.

RESULTS: Mean ± SD preexcision urine AQP1 and ADFP concentrations (76±29 and 117±74 arbitrary units, respectively) in patients with a pathologic diagnosis of clear cell (n=22) or papillary (n=10) cancer were significantly greater than in patients with renal cancer of nonproximal tubule origin, control surgical patients, and healthy volunteers (combined values of 0.1±0.1 and 1.0±1.6 arbitrary units, respectively; n=44; $P<.001$). The AQP1 and ADFP concentrations decreased 88% to 97% in the 25 patients with clear cell or papillary cancer who provided postnephrectomy follow-up urine samples. In patients with clear cell and papillary carcinoma, a linear correlation (Spearman) was found between tumor size and preexcision urine AQP1 or ADFP concentration ($r=0.82$ and 0.76, respectively; $P<.001$ for each).

CONCLUSION: Urine AQP1 and ADFP concentrations appear to be sensitive and specific biomarkers of kidney cancers of proximal tubule origin. These biomarkers may be useful to diagnose an imaged renal mass and screen for kidney cancer at an early stage.

Trial Registration: clinicaltrials.gov Identifier: NCT00851994

ADFP = adipophilin; AQP1 = aquaporin-1; eGFR = estimated glomerular filtration rate; KIM-1 = kidney injury molecule-1; ROC = receiver operating characteristic

Renal cancer accounts for 3% of malignant neoplasms in adults. In 2008, more than 54,000 cases of kidney cancer were diagnosed, and more than 13,000 deaths occurred in the United States.[1] In 2006, the number of deaths from renal cancer was 26,400 in the European Union[2] and more than 100,000 worldwide.[3] The cost of care for kidney cancer in the United States alone was more than $4.4 billion in 2004, predominantly for inpatient expenditures.[2] One in 70 adults in the United States will develop kidney cancer during their lifetimes according to the Surveillance Epidemiology and End Results Stat Facts Sheets of the National Cancer Institute (http://seer.cancer.gov/statfacts/html/kidrp.html).

Renal cancer is generally silent and frequently fatal. Approximately 80% of kidney tumors are discovered incidentally during abdominal imaging (computed tomography, ultrasonography, or magnetic resonance imaging) performed for unrelated diagnostic reasons.[4-9] When symptomatically diagnosed, renal cancer has already metastasized to lymph nodes or other organs in 30% to 40% of patients.[8] Renal cancer is resistant to chemotherapy, and metastatic disease portends a poor prognosis, with a 2-year survival rate of 18%[2] and a 5-year survival rate of 5% or less.[5]

Early detection provides substantial benefits. If the tumor is confined within the renal capsule at diagnosis, survival can exceed 70%.[5] Additional benefits include opportunities for laparoscopic vs open nephrectomy and partial vs total nephrectomy. Minimally invasive laparoscopic nephrectomy, rather than open laparotomy, enables shorter surgical and hospitalization times, faster recovery, and less blood loss, pain, and disability; preserves renal mass and long-term renal function; and reduces cost.[3] Decreased glomerular filtration rates of patients with renal cancer, attributable in part to age (early 60s) at presentation and comorbidities,[10] and the desire to preserve renal function and minimize future chronic kidney disease[10-15] are additional compelling factors for early diagnosis of renal cancer.

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Currently, there is no diagnostic modality for early detection of renal cancer, other than incidental radiologic discovery, and no method of surveillance of recurrence or response to chemotherapy. Population screening would require higher throughput and lower cost than imaging techniques and haphazard discovery. Biomarkers are easily measured substances that can be used to monitor normal and abnormal biologic function. Unfortunately, there is no existing biomarker for kidney cancer diagnosis and no method for population screening. Currently emerging biomarkers of renal disease or injury, such as neutrophil gelatinase–associated lipocalin and kidney injury molecule-1 (KIM-1),[16-19] do not appear applicable to renal cancer because they lack specificity.

Previous investigations[20-29] that used tissue-based expression assays and proteomic analysis have shown increased expression of proteins in surgically excised renal tumor tissue. On the basis of the potential for urinary excretion or elimination of these up-regulated proteins, we tested the hypothesis that aquaporin-1 (AQP1)[21,23,24,28] and adipophilin (ADFP)[30,31] (adipocyte differentiation-related protein) might be increased in the urine of patients with renal cancer. This investigation quantified urine AQP1 and ADFP concentrations in patients with a renal mass undergoing nephrectomy for a presumptive diagnosis of kidney cancer. Prenephrectomy and postnephrectomy (as a pseudocontrol) concentrations were evaluated, as were preoperative and postoperative concentrations in a comparator group undergoing nonrenal surgery and random urine samples in healthy volunteers.

PATIENTS AND METHODS

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The protocol was approved by the Washington University Institutional Review Board, and all patients gave written informed consent to participate. The protocol design was a prospective cohort study that included nested case cohorts, using a 2 × 2 × 1 design. One group was patients with a renal mass and presumptive diagnosis of renal cancer (n=42), a second group was patients undergoing nonnephrectomy (typically orthopedic) surgery but was selected to closely match the nephrectomy group by age and sex (n=15), and the third group was healthy volunteers (n=19) who provided spontaneously voided spot urine samples. In the nephrectomy group, urine samples were obtained (1) on the day of surgery before nephrectomy (preexcision, reflecting disease) and (2) at the time of a scheduled postsurgical follow-up visit (after excision, typically 1-3 months postoperatively, as a pseudocontrol). Patients who underwent nephrectomy served as their own controls, and comparison of prenephrectomy and postnephrectomy urine samples (Wilcoxon signed rank test) would be expected to reflect the presence or absence of specific tumor proteins excreted in the urine or a significant change in the abundance of normal urinary proteins modified by tumor presence. In the nonnephrectomy patients, urine samples were obtained (1) on the day of surgery and (2) at the time of a scheduled postsurgical follow-up. Follow-up averaged 27 days for the patients with kidney cancer and 32 days for the surgical control patients. Comparison of day of surgery and postoperative urine samples (Wilcoxon signed rank test) in the nonnephrectomy patients controlled for any effects of perioperative events on potential biomarker excretion. We compared the prenephrectomy with the nonnephrectomy urine samples (Wilcoxon rank sum test). We also compared the prenephrectomy urine samples to the healthy volunteers' urine samples (Wilcoxon rank sum test). Comparison of prenephrectomy urine and day of surgery urine samples in nonnephrectomy patients provided an additional evaluation of potential renal cancer biomarkers, whereas comparison of urine from healthy volunteers with that of the prenephrectomy urine samples assessed potential renal cancer biomarker excretion and determined a random population baseline level of biomarker.

Pathology reports obtained postoperatively provided renal tumor type (clear cell, papillary, oncocytoma, or chromophobe), size, grade and stage (TNM), or other diagnosis. Pertinent medical history, age, and sex were recorded, and serum creatinine level was used to calculate the estimated glomerular filtration rate (eGFR) by the Modification of Diet in Renal Disease equation.[32]

The 42 patients with a presurgical presumptive diagnosis of kidney cancer were postoperatively determined to have clear cell carcinoma (n=22), papillary (chromatophilic) carcinoma (n=10), oncocytoma (n=4), and chromophobe renal cell carcinoma (n=1) on the basis of histologic analysis of the excised specimens, and 5 were found to have nonmalignant disease, including cystic nephroma, hemangioma, and plasmacytoma. Of the 32 patients with clear cell and papillary tumors, 24 had stage T1 disease without nodal or metastatic involvement, 2 had stage T2 disease, and 6 had stage T3 tumors. One patient with a T3 tumor had metastatic disease; otherwise, no other metastases or node involvement was noted. Postoperative urine samples were obtained in 15 patients with clear cell carcinoma, 10 with papillary carcinoma, 4 with oncocytoma, the 5 patients with nonmalignant disease, and the 15 nonnephrectomy surgical patients. Seven patients diagnosed as having clear cell kidney cancer, including the one patient with chromophobe renal cell carcinoma and 2 with other nonmalignant disorders, were lost to follow-up.

Urine Analysis

Urine was centrifuged (1800*g* for 10 minutes) to remove debris and was mixed with a protease inhibitor tablet (Roche Diagnostics, Indianapolis, IN) before processing for Western blot analysis or freezing at −80°C. Urinary creatinine concentration was quantified by the Jaffe reaction.[33] Protein from 100 μL of fresh-spun urine was precipitated with 1.5 mL of ice-cold acetone-methanol (1:1), centrifuged, and washed with fresh acetone-methanol (1.5 mL). Precipitated proteins were dissolved in an amount of sodium dodecyl sulfate sample buffer such that 5 μL of sample reflected the amount of urine containing 10 μg of creatinine. Urine samples processed for Western blot were stored at 4°C before analysis. The blocked membranes were incubated with 1:500 dilution of anti-AQP1 (H-55) antibody or a 1:200 dilution of anti-ADFP (H-80) antibody (both from Santa Cruz Biotechnology Inc, Santa Cruz, CA) in blocking buffer that contained 0.1% Tween-20 overnight. After washing, the membranes were incubated with a 1:2000 dilution of donkey anti-rabbit IgG IRDye 680 (LI-COR Biosciences, Lincoln, NE) in blocking buffer with 0.1% Tween-20 for 1 hour. Both AQP1 and ADFP were visualized and quantified using an infrared imager (Odyssey Infrared Imager; LI-COR) and proprietary software. Both AQP1 and ADFP were quantified using arbitrary absorbance units. On each gel, the same 2 preexcision urine samples were analyzed and used to normalize the signal response across all gels run within the same or different days. During the span of 11 gels for AQP1, the variation in the signal of these common samples was 10%, and of 10 gels for ADFP, the variation was 9%.

Statistical Analyses

The Fisher exact test was used to compare sex ratios, smoking status, and eGFRs between groups independently. Analysis of variance was implemented to compare the age of study participants among groups. The urinary AQP1 and ADFP levels are summarized as means ± SDs. The prenephrectomy and postnephrectomy urine samples were compared by the Wilcoxon signed rank test. The Wilcoxon rank sum test and the Kruskal-Wallis test were implemented correspondingly to analyze the differences between and among groups in urinary AQP1 or ADFP levels and also the eGFR, under the consideration of normality and small sample size. Relationships between tumor size and biomarker excretion were evaluated by regression analysis with Spearman rank correlation coefficients reported. Receiver operating characteristic (ROC) curve analysis was implemented to examine the predictive ability of AQP1 and ADFP in detecting renal cancer (clear cell and papillary) from surgical control through logistic regression modeling. Areas under the ROC curve were reported. All tests were 2-sided at a .05 significance level. Analyses were performed using SAS statistical software, version 9.2 (SAS Institute, Cary, NC) and Sigma Stat 3.5 (Systat Software, Point Richmond, CA).

RESULTS

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The 22 patients with clear cell carcinoma, the 10 patients with papillary carcinoma, and the 15 controls undergoing surgery for non–kidney-related issues were statistically indistinguishable by age (3 groups: analysis of variance test P=.51 [Table 1]; clear cell cancer vs control: t test P=.27; papillary cancer vs control: t test P=.41) or by sex (Fisher exact test, 3 groups: P=.30; clear cell cancer vs control: P=.26; papillary cancer vs control: P=.40). There were even age (t test P=.98) and sex (Fisher exact test P>.99) distributions between clear cell and papillary carcinoma groups. Comparatively, healthy volunteers were significantly younger. Differences in serum creatinine levels among the 3 groups were not significant (Kruskal-Wallis test P=.07) (Table 1) and neither were differences between the 2 renal cancer subtypes vs controls (clear cell cancer vs control [P=.09] and papillary cancer vs control: Wilcoxon rank sum test [P=.06]). The eGFR was not different among the 3 groups (Kruskal-Wallis test P=.07) (Table 1) or between the 2 renal cancer subtypes vs the control group (clear cell: Wilcoxon rank sum test P=.09; papillary cancer: Wilcoxon rank sum test P=.06). The frequency of smoking, a risk factor for kidney cancer,[3,34] was not statistically different among the 3 groups (Fisher exact test P=.08) or between those with clear cell cancer vs controls (χ^2 test P=.46) but differed between the papillary cancer and control groups (χ^2 test P=.04). The rate of smoking among the 3

groups was 57% for patients with clear cell cancer, 90% for those with papillary cancer, and 47% for surgical controls. Smoking history of the healthy volunteers was not assessed. Statistical analysis of sex, age, smoking, serum creatinine level, and eGFR was not performed for patients with oncocytoma (n=4), nonmalignant renal mass (n=5), and chromophobe renal cell carcinoma (n=1) because of the small number of individuals involved.

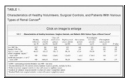

TABLE 1.
Characteristics of Healthy Volulnteers, Surgical Controls, and Patients With Various Types of Renal Cancer[a]

Urine concentrations of both AQP1 and ADFP in patients with renal cancer before tumor excision and in surgical and nonsurgical controls are shown individually in Figure 1 and summarized in Table 2. Representative Western blots for AQP1 and ADFP quantitation are shown in the supplemental data as eFigure 1 and eFigure 2 online linked to this article, respectively. The AQP1 and ADFP concentrations in patients with either clear cell or papillary carcinoma were significantly greater and clearly separated from those in the nonnephrectomy surgical control patients and the healthy individuals. Analysis of the 32 patients with clear cell and papillary cancer and the surgical controls (n=15) bearing no tumor found a significant linear correlation between AQP1 concentration and tumor size (Spearman correlation coefficient = 0.82; $P<.001$; Figure 2). A similar correlation was found for ADFP ($r=0.76$; $P<.001$; Figure 2). If the Spearman analysis is confined to the 32 patients with clear cell and papillary kidney cancer, the correlation coefficient for AQP1 is 0.5 and remains significant at $P=.004$ and .31 for ADFP, but this is not significant at $P=.08$.

FIGURE 1.
Urine aquaporin-1 (AQP1) (left) and adipophilin (ADFP) (right) concentrations in patients with and without renal cancer and in healthy controls. Concentrations were determined by Western blot analysis, expressed in arbitrary density units (AU), and normalized ...

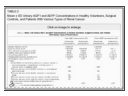

TABLE 2.
Mean ± SD Urinary AQP1 and ADFP Concentrations in Healthy Volunteers, Surgical Controls, and Patients With Various Types of Renal Cancer

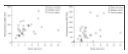

FIGURE 2.
Relationship between tumor size and prenephrectomy urine aquaporin-1 (AQP1) (left) and adipophilin (ADFP) (right) concentrations, expressed in relative density units (RU), in patients with renal carcinoma (papillary cancer, n=22; clear cell cancer, n=10) ...

Four patients with oncocytoma, a benign growth of medullary origin, had preexcision urinary AQP1 concentrations that were statistically indistinguishable from those of the healthy controls and the surgical controls and significantly less than those of the patients with clear cell or papillary tumors. The 6 patients with a radiographically diagnosed renal mass having surgery for a presumptive diagnosis of renal carcinoma but subsequently diagnosed as having cystic nephroma (n=2), plasmacytoma, hemangioma, chromophobe kidney cancer (a malignant variety not of proximal origin), or angiomyolipoma had preexcision urinary AQP1 concentrations that were statistically indistinguishable from those of the healthy controls and the surgical controls and significantly less than those of patients with either clear cell or papillary carcinoma (Table 2). Overall, this pattern of low urinary biomarker excretion before the surgical removal of the tumor was also found to be true for ADFP concentrations in the patients with oncocytoma, nonmalignant renal mass, and chromophobe carcinoma.

The sensitivity and specificity of urine AQP1 and ADFP for detecting renal cancer were determined by ROC curves. The results of AQP1 and ADFP tests in prenephrectomy urine samples of patients with clear cell or papillary renal cancer were considered true positive, and those in surgical controls were considered true negative. Because there is clear separation in relative amounts of both AQP1 and ADFP between the surgical control patients and the cancer patients (Figure 1), area under the ROC curve for each marker is 1.00 (eFigure 3 and eFigure 4 online linked to this article). Therefore, for both AQP1 and ADFP, there was 100% sensitivity and 100% specificity in detecting renal cancer, achievable along a variety of threshold values. It follows that ROC curve analysis between patients with renal cancer and healthy controls is the same as for the surgical controls (data not shown).

Of the 33 patients in the study with a diagnosis of renal carcinoma, 15 with clear cell and all 10 patients with papillary carcinoma returned for a surgical follow-up visit (average of 27 days) postoperatively and provided a urine sample, as did all the 15 surgical controls (average of 32 days). Urinary AQP1 and ADFP concentrations in the postoperative urine samples of the patients with renal cancer, after tumor removal, were significantly decreased compared with those of the preexcision urine samples (Figure 3 and Table 2). There was a 95% decrease in urinary AQP1 concentration and an 88% decrease in ADFP concentration in the 15 patients with clear cell carcinoma. After tumor excision, there was a 97% decrease in AQP1 concentration and a 92% decrease in ADFP concentration in the 10 patients with papillary renal carcinoma.

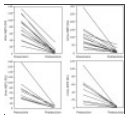

FIGURE 3.
Change in urinary aquaporin-1 (AQP1) (left) or adipophilin (ADFP) (right) concentrations, expressed in relative density units (RU), after partial or total uninephrectomy in patients with clear cell renal carcinoma (n=15, top) or papillary carcinoma (n=10, ...

DISCUSSION

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Results of this investigation show that urine concentrations of AQP1 and ADFP are significantly increased in patients with clear cell or papillary carcinoma compared with concentrations in a control group of patients undergoing nonnephrectomy surgery, a control group of healthy volunteers, and patients with oncocytoma (benign medullary tumor). The AQP1 and ADFP concentrations diminished significantly after tumor removal (postnephrectomy group), a pseudocontrol, demonstrating the renal tumor origin of these urine proteins. Postoperative AQP1 and ADFP concentrations in the nonnephrectomy surgical patients were unchanged from preoperative concentrations, showing that the postoperative change in the patients with renal cancer was not an artifact of anesthesia or surgery.

Together, these findings strongly support the proof of concept that urine concentrations (normalized to creatinine excretion) of the

proteins AQP1 and ADFP are sensitive, specific, and noninvasive biomarkers for the diagnosis of renal clear cell and papillary cancers. These 2 tumor types, which arise from the proximal tubule, together account for approximately 90% of all renal cancers.[2,5,8] The AQP1 concentrations reflected tumor burden, estimated from excised tumor size. Previous studies have found that transcript expression for both AQP1[21] and ADFP[30,31] decreased as tumor stage increased. In the current investigation, only 7 of the 32 patients with clear cell and papillary carcinoma had stage 2 or 3 disease. This is an insufficient number of higher-stage tumors to provide meaningful conclusions about urinary biomarker concentrations and disease severity. In addition, gene expression may not be a parallel indicator of anticipated protein expression. Oncocytomas, which account for a small fraction (5%) of renal cancers and which arise from collecting duct cells, were not associated with increased AQP1 and ADFP elimination. Of note, patients who had renal masses diagnosed by incidental radiologic findings or clinical symptoms but who did not have cancers of the proximal tubule had normal urine AQP1 and ADFP excretion.

Aquaporin-1 is a water channel protein present in the apical membrane of the proximal tubule but can increase the migration and metastatic potential of tumor cells.[35] Aquaporin-1 was found by expression array analysis of excised renal tumors to have increased expression.[21,23,24,28] To our knowledge, this is the first report of increased urine AQP1 excretion in patients with renal cancer.

Adipophilin is a protein associated with lipid droplets,[36] a prominent pathologic feature of clear cell carcinoma[37] and those of macrophages.[38,39] Lipid droplets, in addition to accumulated glycogen granules, account for the histologic clearness of the cells. Moreover, papillary carcinomas are associated with abundant lipid-laden macrophages.[37] Expression of ADFP was found to be up-regulated in surgically excised renal tumor tissue.[30,31,40,41] To our knowledge, this is the first report of increased urine ADFP excretion in renal cancer.

In addition to being expressed in most kidney cancers,[30,31,40,41] ADFP has target epitopes for possible antigen-specific cytotoxic T-lymphocyte–mediated immunotherapy.[42,43] Interestingly, patients with kidney cancer who were immunized with MUC1 peptide–pulsed dendritic cells displayed epitope spreading and showed reactivity of their monocyte-derived dendritic cells toward ADFP.[43] It remains unknown whether urinary ADFP could also be of prognostic value.

There are many expression or tissue microarray studies that characterize potential biomarkers of renal cancer[20-29]; however, these studies have not yielded any candidate markers for testing in urine. Only a few studies have examined urine as a potential source of biomarkers for renal cancer, and these focused on fragments of uromodulin and serum amyloid A[25,27,44] or undefined proteins uncovered by mass spectrometry.[44] Many of the proposed markers studied to date, although expressed in high frequency in patients with kidney cancers, are also expressed in patients with other cancers[17,26,29] or kidney diseases.[16,19,45,46] This mutes their specificity, which is required of a kidney cancer biomarker. In addition to urine proteins, the urinary metabolomic profile has been considered as a source of potential biomarkers of kidney cancer.[47] However, a recent study found that the qualitative and quantitative pattern of urinary metabolites was influenced by patient diet, time of day of sample collection, and area of the country of the participating sites and that it could not reliably distinguish urinary metabolites of the same patient before tumor excision compared with after tumor excision.[22] This casts doubt on the current reliability of metabolomics as a diagnostic approach to screen even at-risk populations for kidney cancer.

Another promising biomarker of renal injury is KIM-1, which is also undergoing clinical evaluation. By immunohistochemical analysis, KIM-1 expression was significantly increased in clear cell and papillary carcinoma and not present in adjacent healthy kidney.[16,17] Urinary KIM-1 excretion was increased in patients with clear cell or papillary tumors, and the urine KIM-1 excretion mirrored tumor size.[16] This further supports the proof of principle that urine from patients with kidney cancer can contain specific protein(s) in concentrations different from that in unaffected patients. That KIM-1 is found in increased amounts in urine from patients with these renal tumors is additionally important because these renal tumors are partially or completely surrounded by a fibrous capsule.[48,49] This suggests communication of the renal tumors with the urine-forming tubular elements of the kidney, which further supports the use of urine as a source to discover and measure biomarkers specific for kidney cancer. Nevertheless, KIM-1 is also overexpressed and excreted in the urine from patients with numerous types of kidney injury, such as that due to diabetes mellitus, glomerulosclerosis, IgA nephropathy, nephrotoxicants, and ischemic injury.[19,45,46] Thus, it is a nonspecific biomarker of any kidney injury and lacks the specificity needed for a biomarker of kidney cancer.

Findings of the current investigation, although promising, are early in the development timeline of clinical biomarkers. Urine AQP1 and ADFP samples were quantified by Western blot analysis and in a small clinical investigation; however, absolute quantification with higher throughput awaits development of enzyme-linked immunosorbent assay or other suitable assays. Although the decrease in urinary AQP1 and ADFP levels was substantial after tumor removal, concentrations in the postexcision urine samples were somewhat greater compared with those found in the surgical control patients. Currently, no explanation exists for this observation. One possibility may be some residual tumor effect on the remaining normal kidney tissue. The small amount of urinary ADFP excretion seen in the surgical control patients compared with that in the healthy volunteers is similarly unexplained. One untested possibility may be age differences between these 2 groups.

Despite these acknowledged limitations, urinary AQP1 and ADFP levels appear to be sensitive, selective, and useful biomarkers for renal cancer. Potential clinical applications include specific diagnosis of renal clear cell or papillary cancer after discovery of an imaged renal mass and weighing treatment options,[10] population screening for renal cancer, and possibly surveillance for recurrence after or during treatment. Thus, a viable implementation might be widespread, annual (or other appropriate interval) population screening for renal cancer in at least at-risk populations. Another value of urinary AQP1 and ADFP levels may lie in the predictive value of a negative test result. For example, the current standard of care for a renal mass found during incidental radiologic examination is prompt nephrectomy because cancer is presumed, and no test is available to characterize the mass as cancerous vs noncancerous. On computed tomography, clear cell carcinomas and oncocytomas have overlapping features and can be difficult to distinguish.[50] Urinary AQP1 and/or ADFP levels may be applied as a follow-up to a radiologic finding to help diagnose cancer vs benign renal tumor. If the latter is found, an unnecessary nephrectomy may be obviated, or at least watchful waiting may be possible. Clearly, further investigation is needed to define and validate the clinical applications for use of urinary ADFP and AQP1 measurement in the diagnosis and evaluation of renal cancers.

CONCLUSION

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Urine from patients with kidney clear cell or papillary carcinomas contains specific tumor-related proteins at increased

concentrations compared with that from surgical control patients or healthy volunteers. These proteins, AQP1 and ADFP, appear to be sensitive and specific biomarkers of cancers that originate in the kidney proximal tubule. Independent validation and further study are needed.

Supplementary Material

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eFigures:

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Acknowledgments

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Footnotes

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This investigation was supported by funds from the Department of Anesthesiology, Washington University in St Louis.

Washington University has filed a patent application for use of aquaporin-1 and adipophilin to diagnose renal cancer.

An earlier version of this article appeared Online First.

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