

The long-term outcomes of percutaneous therapy for renal artery fibromuscular dysplasia

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Background: Percutaneous intervention for symptomatic renal artery fibromuscular dysplasia (FMD) has replaced surgical therapy as first-line treatment. This study evaluates the factors that impact long-term anatomic and functional outcomes of endovascular therapy for symptomatic renal artery FMD.

Methods: Records of patients who underwent renal artery angioplasty for FMD between January 1990 and December 2007 were retrospectively analyzed. Indication for intervention was poorly controlled hypertension (diastolic blood pressure >90 mm Hg or systolic blood pressure >140 mm Hg, or both, taking >2 antihypertensive medications). Twenty-nine women (average age, 45 years [range, 18-80]; 86% with a history of hypertension <8 years) underwent 38 attempted interventions. Sixty-six percent of contralateral kidneys were normal (31% had a $\leq 60\%$ stenosis), 13% had >60% stenosis, and the remainder were nonfunctioning or absent. Creatinine was >1.5 mg/dL in 4%, 24% had hyperlipidemia, 17% had metabolic syndrome, and 4% were considered diabetic.

Outcomes: All interventions were successfully performed. Stent placement was required in 13% for technical failure and flow-limiting dissection. Seventy-three percent of these lesions were in the proximal renal artery, with the remainder in the middle renal artery. Technical success (<30% residual stenosis) was achieved in all vessels. There were no periprocedural or 90-day deaths. The procedurally related complication rate was 8%. Median follow-up was 2 years. All patients were alive at follow-up. Primary and assisted primary patency rates were 66% and 87% at 5 years. Restenosis was considered a 50% reduction in luminal area on angiography during follow-up. The restenosis rate was 28% at 5 years (10 vessels underwent repeat percutaneous intervention). Immediate clinical benefit was seen in hypertension in 72% (improved or cured ≤ 3 months) and was maintained in 73% at 5 years by life-table analysis. Proportional hazard analysis showed the predictors of long-term clinical benefit were duration of hypertension <8 years, creatinine <1.5 mg/dL, ipsilateral kidney size >9 cm, functional status of the contralateral kidney, a fasting blood glucose <110 mg/dL, triglycerides <150 mg/dL, and high-density lipoprotein >50 mg/dL. Neither age <50 years nor statin administration appeared significant.

Conclusions: Percutaneous endovascular intervention for clinically symptomatic FMD in the renal arteries is technically successful, safe, and durable. Most patients have immediate clinical benefit, with continued long-term results out to 5 years. It appears that the presence of existing renal pathology and markers of prediabetic state are associated with recurrence of hypertensive symptoms. (J Vasc Surg 2008;48:865-71.)

Fibromuscular dysplasia (FMD) can result in significant hypertension in women aged between 15 and 50 years old but only accounts for <10% of cases of renovascular hypertension.¹ First described in 1938,² FMD frequently involves the distal main renal artery and its branches.¹ Medial fibroplasia represents the most common dysplastic lesion. Medial hyperplasia may be indistinguishable angiographically from intimal fibroplasia. Intimal fibroplasia occurs in <10% of patients with arterial fibrodysplasia. Adventitial (periarterial) hyperplasia is the rarest type of fibrodysplastic lesion.

Although FMD has been shown to affect multiple arterial beds, the frequency of involvement in renal arteries is 60% to 70%, with bilateral disease occurring in 35% of

patients. The natural history of renal FMD is progression in up to 37% of patients,³ but this progression only rarely results in occlusion of the renal artery.⁴ Patients with FMD do demonstrate a significant decrease in mean cortical thickness and reduced renal length compared with similar patients with essential hypertension. As many as 63% of patients with FMD experience a loss of renal mass, but the incidence of renal failure remains remarkably low.^{3,5} Renal artery atherosclerosis, in contrast, is a significant cause of progressive renal dysfunction leading to ischemic nephropathy and loss of functioning renal mass.⁶

The main impetus for the treatment of FMD is control of hypertension and its attendant complications. The treatment for most patients can be primarily managed medically. Revascularization is reserved for those patients who have recent onset of hypertension (<1 year), with the primary goal to cure the hypertension, those in whom blood pressure control has proved difficult, those intolerant of antihypertensive therapy, those who are not compliant with their antihypertensive medication, and those who have demonstrated a loss of renal volume leading to a diagnosis of ischemic nephropathy.⁷

The primary mode of intervention is by balloon angioplasty, with surgery reserved for recalcitrant lesions. Few

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reports, however, address the factors that affect the long-term durability or clinical effectiveness of percutaneous transluminal renal angioplasty (PTRA) for renal artery FMD. The purpose of this study is to evaluate the factors that influence the long-term anatomic and functional outcomes of endovascular therapy for symptomatic renal artery FMD.

METHODS

Study design. We performed a retrospective analysis of records from patients who underwent PTRA for all causes between January 1990 and December 2007, and those with FMD of the main renal artery were identified. Patients with aneurysmal disease and branch vessel disease were excluded. Indication for intervention was poorly controlled hypertension, defined as diastolic blood pressure (DBP) >90 mm Hg or systolic blood pressure (SBP) >140 mmHg, or both, taking >2 antihypertensive medications. For each patient, demographics, existing comorbid conditions, and risk factors for atherosclerosis were identified. Freedom from recurrent hypertension and factors influencing clinical benefit were measured.

Treatment algorithm. Patients with hypertension underwent a diagnostic study to identify the presence of renal artery stenosis. Procedures were performed within a service line, and interventionalists were drawn from vascular surgery, interventional cardiology, and interventional radiology. This diagnostic study consisted of standard angiography, magnetic resonance angiography (MRA), renal isotope scan, or duplex ultrasound (DUS) imaging. The DUS criteria to identify renal artery stenosis has been previously described.⁸⁻¹⁰ Angiography was performed in the presence of clinical criteria as defined by Rundback et al¹¹ and a $\geq 60\%$ stenosis on DUS or MRA or a positive renal scan.

The angiographic analysis was generally performed through a femoral or transaxillary approach. The lesions were crossed with a soft, atraumatic guidewire through an SOS Omni or Simmons catheter (Angiodynamics, Queensbury, NY). Balloon angioplasty was performed under systemic heparinization (40 to 60 U/kg intravenously), with the use of a 0.035-inch guidewire and 4- to 7-mm balloons. A balloon size 10% larger than the renal artery diameter was typically selected. Guiding catheters were used when extra support was deemed necessary. Primary stenting was not used in this series. Stenting was only used for technical failure and flow-limiting dissection.

Interventions were performed in patients with renal artery stenosis $\geq 50\%$ by angiography, regardless of comorbidities. The treatment of patients not categorized into the clinical criteria referenced was managed medically. Nonfunctioning kidneys were not treated. In the presence of bilateral disease, the clinical criteria for treatment of both kidneys were the same as those for solitary renal artery stenosis. Bilateral >50% disease was treated at the same setting.

Patients were followed up at 6-month intervals after the procedure. Blood pressure, serum creatinine level, and number of antihypertensive medications were identified

during these intervals. To assess postprocedural patency, each patient had at least one DUS study ≤ 1 month, a second at 6 months, and a DUS evaluation every 6 months thereafter. If the DUS showed $\geq 60\%$ stenosis and the patient had recurrent symptoms of poorly controlled hypertension (DBP >90 mm Hg or SBP >140 mm Hg, or an increase in antihypertensive medications >2), angiography was performed and restenosis was treated if it was $\geq 50\%$. Median follow-up was 2 years (mean, 3.3; range 0.7-14.4 years) with a median of 4 DUS scans (range, 2-98 scans).

Definitions. The definitions used in the study are as follows:

- Coronary artery disease was defined as a history of angina pectoris, myocardial infarction, congestive heart disease, or prior coronary artery revascularizations.
- Cerebrovascular disease included a history of stroke, transient ischemic attack, or carotid artery revascularization.
- Hypercholesterolemia was defined as a fasting cholesterol level >200 mg/dL.
- Diabetes was defined as a fasting plasma glucose level >110 mg/dL or an HbA_{1c} >7%. Patients with diabetes were characterized as having insulin-dependent diabetes mellitus or non-insulin-dependent diabetes mellitus.
- Hypertension was defined as a SBP >140 mm Hg or DBP >90 mm Hg on three occasions during a 6-month period.
- Metabolic syndrome was defined as previously described,¹² consisting of insulin resistance or impaired glucose tolerance, hypertension, dyslipidemia, and abdominal obesity, with the exception of abdominal circumference, which was not routinely recorded. We substituted a body mass index score ≥ 30.0 kg/m² as a positive score instead of an abdominal circumference >102 cm for men or >88 cm for women.
- An elevated serum creatinine level was defined as ≥ 1.5 mg/dL on two consecutive values during a 3-month period.
- Chronic renal insufficiency was defined as a persistent serum creatinine level >1.5 mg/dL for >6 months.
- Estimated glomerular filtration rate (eGFR) was defined as $186.3 \times \text{serum creatinine}^{-1.154} \times \text{age}^{-0.203} \times 0.742$ (if female) $\times 1.212$ (if African American). The baseline serum creatinine was the value recorded closest to the procedure.

Patients were considered to have a "nonfunctioning kidney" if any two of the following local criteria used at our institution during the study period were met: (1) a DUS scan identified a pole-to-pole length of <9 cm, with no renal flow in the main renal artery and parenchymal peak systolic velocity <10 cm/s, (2) surgically or congenitally absent kidney, or (3) no visible nephrogram on contrast arteriogram. The renal resistive index was defined from DUS imaging as $(1 - [\text{end diastolic velocity/peak systolic velocity}]) \times 100$.

An endoluminal procedural success was a residual stenosis of $<30\%$. Failures were residual stenosis $\geq 30\%$, by angiographic measurement, including lesions unable to be dilated or crossed, and occlusion ≤ 30 days. Restenosis was considered a 60% reduction in luminal area as determined by DUS imaging or a 50% reduction in luminal area as determined by angiography, or both, during follow-up. A death ≤ 30 days of the procedure was considered procedurally related.

Response in the hypertensive patient was defined as follows: "Cured" patients became normotensive after intervention (DBP <90 mm Hg and SBP <140 mm Hg) without medications. "Improved" patients became normotensive after intervention (DBP <90 mm Hg or SBP <140 mm Hg, or both) on the same (or reduced) number of medications, or had a DBP 15 mm Hg below baseline with the same or reduced number of medications. "No effect" patients had no change or did not meet these criteria for cure or improvement of presenting hypertension after intervention and were considered a treatment failure. For the purposes of this report, responders were patients in whom an improved or cured hypertension was demonstrated ≤ 3 months of intervention, and nonresponders were patients in whom no effect on their hypertension was demonstrated. Recurrence of hypertension was defined as a recurrence of DBP >90 mm Hg or SBP >140 mm Hg, or a $>20\%$ increase of postprocedural baseline DBP that was not treatable by repeat angioplasty.¹¹

Statistical analysis. We performed our analysis on an intention-to-treat basis. Measured values are reported as percentages or means ± 1 standard deviation. Survival, cumulative patency, and clinical benefit rates are calculated using life-table analysis and reported using the Society for Vascular Surgery criteria. Standard errors are reported in life-table analyses. The log-rank test was used to determine differences between life tables. The Cox proportional hazards model was used for the time-dependent outcomes of death, patency, and long-term freedom from recurrent hypertension. The proportional hazards assumption was checked and confirmed for the significant covariates using log (-log [survival]) curves. Logistic regression models were used for outcomes measured shortly after the procedure, including complications and short-term clinical benefits. The dependence of each covariate on the outcome was first checked separately using the χ^2 test. Covariates with the significance level of $P \leq .10$ were included in the multivariate stepwise analysis.

RESULTS

Patient population. The study comprised 29 women who were a mean age of 45 years (range 18-80 years), with 69% were aged <50 years. A total of 38 interventions were attempted (9 were for bilateral lesions). A history of hypertension <8 years was present in 86%, 24% had hyperlipidemia, 17% had metabolic syndrome, 4% were considered diabetic, and 4% had a serum creatinine level >1.5 mg/dL (Table I). Sixty-six percent of contralateral kidneys were

Table I. Patients characteristics, indications, and comorbidities by response to treatment

Characteristics	Response	No Response	P
Patients, No.	21	8	...
Kidneys treated, No.	27	11	...
Bilateral disease, No.	6	3	...
Age			
Mean average $\pm$ SD, years	47 $\pm$ 16	43 $\pm$ 22	.02
<50 years, %	71	63	.09
Hypertension duration <8 years, %	86	63	$<.05$
Blood pressure, mean $\pm$ SD mm Hg			
Systolic	169 $\pm$ 20	180 $\pm$ 36	.2
Diastolic	92 $\pm$ 13	91 $\pm$ 14	.3
Antihypertensive drugs, mean $\pm$ SD	2 $\pm$ 1	3 $\pm$ 1	.5
Comorbidities, %			
Smoking history	19	13	.09
Diabetes mellitus	5	0	$<.05$
Hyperlipidemia	19	38	$<.05$
Metabolic syndrome	14	25	$<.05$
Cerebrovascular	10	13	.2
Creatinine >1.5 mg/dL	5	13	$<.05$
Hormone replacement therapy	10	8	.12
Metabolic syndrome variables, %			
Hypertension	100	100	
Body mass index >27 kg/m ²	28	13	$<.05$
Fasting blood glucose ≥ 110 mg/dL	19	25	$<.05$
HDL ≤ 50 mg/dL	13	35	$<.05$
Triglycerides ≥ 150 mg/dL	19	25	$<.05$

HDL, High-density lipoprotein; SD, standard deviation.

normal (31% had a $\leq 60\%$ stenosis), 13% had $>60\%$ stenosis, and the remainder were nonfunctioning or absent (Table II).

Immediate outcomes (<3 months). Of the 38 planned interventions, technical success, as defined by $<30\%$ residual stenosis on angiographic imaging, was achieved in all vessels; however, placement of a stent occurred in 13% because of technical failure and flow-limiting dissection. The proximal renal artery was the location for 73% of these lesions, with the remainder in the middle renal artery. No branch vessels of the main renal artery were treated. There were no periprocedural 30-day or 90-day deaths.

The procedure-related complication rate was 8%; all were minor and included one patient each with groin hematoma, groin pseudoaneurysm, and arteriovenous fistula. Hypertension was "improved" or "cured" ≤ 3 months of intervention in 72% of the patients (Table III). Significant differences were seen in the population of responders vs nonresponders in duration of hypertension (<8 years), presence of hyperlipidemia, worsening stage of chronic kidney disease, smaller ipsilateral kidney, contralateral renal artery stenosis ($>50\%$), and bilateral higher resistive indices within the kidney (Tables I and II). These factors all correlated with response. When we specifically looked at metabolic syndrome as a discrete variable, it was not signifi-

Table II. Kidney disease, functional parameters, and ipsilateral and contralateral variables according to response to treatment

Variable	Response	No response	P
Kidney stage, %			
1 (eGFR $\geq 90^a$)	29	38	.1
2 (eGFR 60-89 ^a)	52	25	<.05
3 (eGFR 30-59 ^a)	19	25	<.05
4 (eGFR 15-29 ^a)	0	13	<.05
5 (eGFR <15 ^a or dialysis)	0	0	
Functional parameters			
Creatinine, mean $\pm$ SD mg/dL	0.9 $\pm$ 0.01	1.3 $\pm$ 0.1	<.05
eGFR, mean $\pm$ SD ^a	78.0 $\pm$ 1.1	74.6 $\pm$ 4.3	
eGFR <30 ^a , %	0	13	<.05
eGFR 30-60 ^a , %	24	12	<.05
eGFR >60 ^a , %	76	75	.2
Ipsilateral kidney variables			
Kidney size, mean $\pm$ SD cm	10.4 $\pm$ 0.04	9.7 $\pm$ 0.05	<.05
Resistive index, mean $\pm$ SD	0.65 $\pm$ 0.004	0.70 $\pm$ 0.01	<.05
Contralateral kidney anatomy, %			
Normal	71	50	<.05
Stenosis (>60%)	19	50	<.05
Nonfunctioning	10	0	<.05
Contralateral kidney variables			
Kidney size, mean $\pm$ SD cm	9.6 $\pm$ 0.02	9.6 $\pm$ 0.1	.3
Resistive index, mean $\pm$ SD	0.66 $\pm$ 0.005	0.68 $\pm$ 0.01	<.05

eGFR, Estimated glomerular filtration rate; SD, standard deviation.

^aThe eGFR is calculated as mL/min/1.73 m².**Table III.** Outcomes according to response to treatment

Outcome	Response	No response	P
Immediate clinical benefit, %			
Deterioration	0	0	
No Change	0	100	<.05
Improved	81	0	<.05
Cured	19	0	<.05
Long-term outcomes, %			
Vessel occlusion	0	38	<.05
Vessel restenosis	14	13	.2
Absolute recurrence	14	25	<.05
Ipsilateral reintervention	14	13	.2

icantly associated with poor outcomes when all-comers were identified; however, when the group was stratified, more patients in the nonresponder group were diagnosed as having metabolic syndrome, and the predominant features were abnormal fasting blood glucose, low high-density lipoprotein (HDL), and elevated triglycerides (Table I).

Outcomes (>3 months). All patients were alive at follow-up. No chronic renal impairment developed during follow-up. Primary and assisted primary patency rates determined by serial DUS imaging were 66% and 87% at 5 years (Fig. A). Assisted primary and secondary patency rates were equal (Fig. A). The restenosis rate was 28% at 5 years (Fig. B). Stent placement did not influence patency, restenosis, or symptom recurrence. Ten vessels underwent repeat percutaneous intervention for recurrent symptoms. Reintervention by balloon angioplasty for restenosis in those patients with recurrent symptoms, defined as poorly controlled hypertension (DBP >90 mm Hg or SBP >140

mm Hg or an increase in antihypertensive medications of >2), was successful in all cases.

Development of restenosis was associated with low HDL levels (≤ 50 mg/dL, female; relative risk [RR], 2.35; 95% confidence interval [CI], 1.32-4.52; $P = .004$); elevated triglycerides levels (≥ 150 mg/dL; RR, 2.2; 95% CI, 1.84-2.86; $P = .004$); eGFR <30 mL/min/1.73 m² (RR, 1.74; 95% CI, 1.09-3.24; $P = .004$); and age >55 years (RR, 2.78 (95% CI, 1.51-131.50; $P < .003$).

In response to therapy, 72% of patients demonstrated immediate clinical benefit, with improved or cured hypertension ≤ 3 months of procedure. This clinical benefit was maintained in 71% $\pm$ 9% of patients at 5 years by life-table analysis (Fig. C). When only those patients who demonstrated immediate clinical benefit were analyzed, clinical benefit was maintained in 73% $\pm$ 9% at 5 years by life-table analysis. A significant relationship was found between the presence of restenosis and loss of clinical benefit (odds ratio, 0.008; 95% CI 0.0004-0.167; $P < .0001$). Angiographically significant restenosis was found in only 64% of patients with recurrent symptoms (odds ratio, 0.0084; 95% CI, 0.0004-0.1658). We did not encounter any patients with asymptomatic restenosis during follow-up.

Proportional hazard analysis showed the predictors of long-term clinical benefit were duration of hypertension <8 years (RR, 1.23; 95% CI, 1.01-2.98, $P = .02$), eGFR >60 mL/min/1.73 m² (RR, 26.5; 95% CI, 18.1-34.5, $P = .01$), ipsilateral kidney size >9 cm (RR, 1.41; 95% CI, 1.1-3.3; $P = 0.03$), status of the contralateral kidney (RR, 1.53; 95% CI, 1.1-1.96, $P = .04$), a fasting blood glucose <110 mg/dL (RR 1.53, 95% CI 1.17-2.34, $P = .04$),

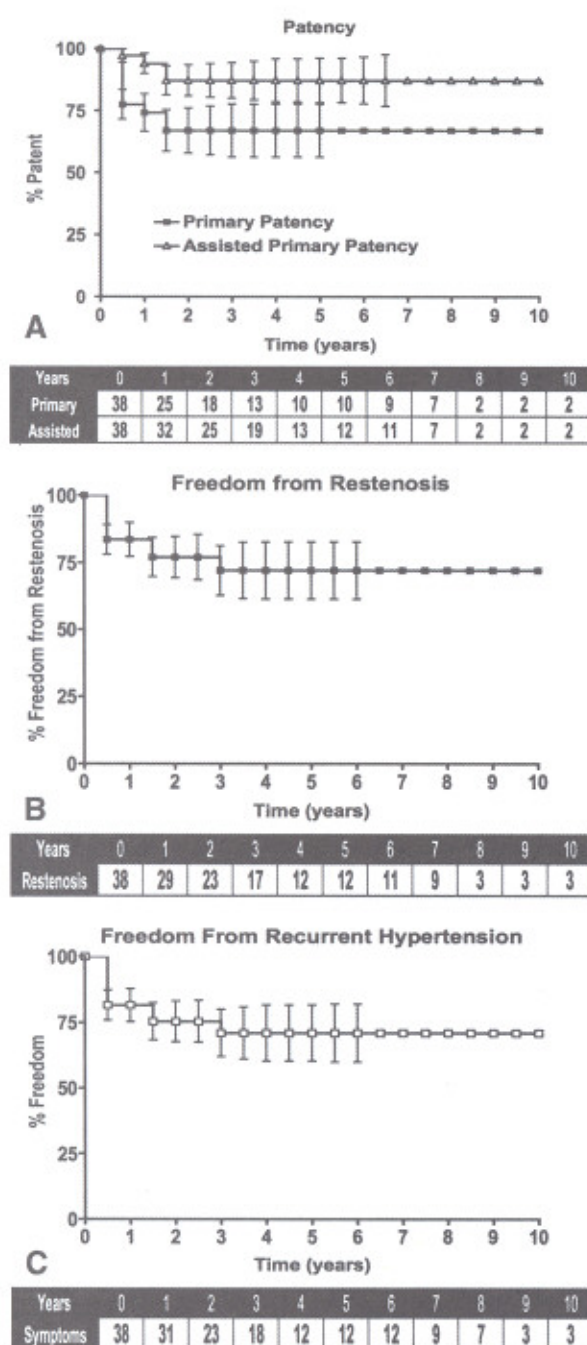


Fig. A, Life-table analysis of primary and assisted primary patency of the renal vessels intervened on for symptomatic fibromuscular dysplasia. B, Life-table analysis of freedom from restenosis. C, Life-table analysis of freedom from recurrent hypertension. Recurrence was defined as a recurrence of diastolic blood pressure >90 mm Hg or systolic blood pressure >140 mm Hg or a $>20\%$ increase of postprocedural baseline diastolic blood pressure that was not treatable by repeat angioplasty. Values are mean $\pm$ standard error of the mean. The number at risk at each time interval is shown below each figure.

triglycerides <150 mg/dL (RR 6.67, 95% CI 1.86-10.03, $P = .004$), and HDL >50 mg/dL (RR 3.89, 95% CI 2.12-6.39, $P = .024$); the latter three are markers of the prediabetic state and associated with metabolic syndrome. Neither age <50 years nor administration of statins appeared to be significant. Categorization of the status of the contralateral kidney by occlusion of the renal artery vs surgically absent kidney did not influence freedom from recurrent symptoms.

DISCUSSION

PTRA has become the treatment of choice for patients with renal artery FMD limited to the main renal artery.³ Most these patients have medial fibroplasia. In the current cohort of patients with FMD and hypertension, PTRA was technically successful and was associated with no major complications and a low morbidity rate. There was a 100% technical success rate, whereas published reports indicate technical success rates for PTRA in these circumstances of 83% to 100%.¹³⁻¹⁹ Success rates with open revascularization are 89% to 97%. No anatomic injuries or acute functional injuries occurred. In contrast with the FMD population, acute functional injury, defined as a persistent increase in the serum creatinine level of ≥ 0.5 mg/dL at 1 month after the procedure, associated with atheroembolism during renal intervention for atherosclerotic disease, is now recognized as an important clinical problem.²⁰⁻²² Patient survival in this cohort was 100% during follow-up, no new patients developed chronic renal impairment, and those with a pre-existing serum creatinine level >1.5 mg/dL did not demonstrate worsening of renal function.

We had a 100% technical success rate after intervention according to angiographic criteria. One caveat on this result should be mentioned. Currently, many authors now recommend that because the degree of stenosis associated with FMD cannot always be estimated by angiographic appearance alone, transluminal pressure measurements or immediate postprocedural duplex sonography, or both, should be performed to better describe technical success.

The current study showed a cumulative patency rate 87% at 5 years. Restenosis developed in 14% of the vessels, with an actuarial restenosis rate of 28% at 5 years. Reintervention by balloon angioplasty for restenosis was successful in all cases. Reported restenosis rates after PTRA for FMD are 7% to 27%.¹³⁻¹⁹ Clinical factors associated with restenosis after initial PTRA, include increased body mass index and duration and degree of hypertension.²³ We did not identify either factor as a significant variable in the development of restenosis.

Oertle et al²⁴ have shown that about one-third of patients treated by PTRA for FMD who subsequently return during follow-up with deterioration of or recurrent arterial hypertension have no angiographic demonstrable restenosis, whereas 15% of patients without deterioration of or recurrent arterial hypertension have angiographic demonstrable restenosis. Our data confirmed that approximately one-third of patients with recurrent symptoms do not demonstrate restenosis and that the presence of restenosis in asymptomatic patients is very low. However, the

relatively high rate of occlusion in the nonresponders should prompt early reimaging of the renal vessel and should prompt more frequent duplex imaging.

Diabetes and insulin resistance have been shown to be independent predictors of early restenosis after coronary stenting.²⁵⁻²⁸ In the current study, dyslipidemia (low HDL and high triglyceride levels), low eGFR (<30 mL/min/ 1.73 m²), and patients aged >55 years were factors associated with the development of restenosis.

The clinical success, defined as cured or improved hypertension after PTR, was 72%. Hypertension cure rates of 14% to 59% and hypertension improvement rates of 21% to 63% have been reported.¹³⁻¹⁹ The incidence of "no effect" with endoluminal intervention ranges from 7% to 30%.³ With open surgery, cure of hypertension can be obtained in 33% to 63% of patients, with improvements in hypertension noted in 24% to 57%. The incidence of failure (ie, "no effect" on hypertension) is 3% to 33%. Successful outcome appears to be associated with an age <50 years, the absence of associated coronary and carotid stenosis, and duration of hypertension of <8 years. In the current study, we identified the duration of hypertension as a significant factor related to successful outcome. However, we also identified an association with decreased long-term clinical benefit and a cluster of variables associated with prediabetic state, including fasting blood glucose >110 mg/dL, triglycerides >150 mg/dL, and HDL ≤ 50 mg/dL. This is a novel finding. An important finding in this cohort was that statin therapy did not influence outcomes.

These data would suggest that surveillance for and aggressive correction of both the prediabetic state and dyslipidemic should be considered in patients presenting with symptomatic FMD. There are limitations to the current study. The patient number is relatively small but does represent one of the largest series in the literature. We only treated main renal artery disease and did not include patients with branch vessel disease.

CONCLUSION

Percutaneous endovascular intervention for clinically symptomatic FMD in the main renal artery is technically successful and safe. There are excellent cumulative patency and low restenosis rates. Most patients experience an immediate clinical benefit, with continued long-term results in $>70\%$. It appears that the presence of existing renal pathology and markers of prediabetic state are associated with restenosis and with recurrence of hypertensive symptoms.

AUTHOR CONTRIBUTIONS

Conception and design: MD
Analysis and interpretation: WS, MD
Data collection: EP, IM, JN, WS, AL, MD
Writing the article: WS, AL, MD
Critical revision of the article: EP, IM, JN, WS, AL, MD
Final approval of the article: EP, IM, JN, WS, AL, MD
Statistical analysis: WS, MD
Obtained funding: MD
Overall responsibility: MD

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The Epidemiology of Renal Cell Carcinoma

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Purpose: We identified and examined risk factors for renal cell cancer, some of which may explain in part the trends of steadily increasing incidence rates, particularly in black Americans.

Materials and Methods: Epidemiological studies were identified through a MEDLINE® search of the literature through February 2006. A qualitative summary of the results of individual studies is presented.

Results: Cigarette smoking and obesity are the most consistently established causal risk factors, accounting for about 20% and 30% of renal cell cancers, respectively. Hypertension appears to independently influence renal cell cancer risk. Neither acetaminophen nor other analgesics have been convincingly linked with renal cell cancer. With respect to diet a general protective effect of fruit and vegetable consumption is the only consistently reported finding. For occupational factors the weight of the evidence provides no consistent support for the hypotheses that renal cell cancer may be caused by asbestos, gasoline or trichloroethylene exposure. Self-reported family history is associated with 2 to 3-fold increases in risk and the major inherited forms of renal cell cancer together account for about 2% of this malignancy.

Conclusions: A further reduction in cigarette smoking, and a decrease in the rates of obesity and hypertension would likely moderate the increasing incidence of renal cell cancer. Epidemiological studies, including evaluation of gene-environment interactions, are needed to specifically identify reasons for the increasing incidence, particularly for assessing the roles of obesity and hypertension. Special attention should be focused on black Americans since their incidence rate recently increased to significantly surpass that in white Americans.

Key Words: kidney; kidney neoplasms; carcinoma, renal cell; epidemiology; risk factors

Kidney cancer accounts for about 2% of all new cancer cases worldwide¹ with 38,890 cases and 12,840 deaths expected in 2006 in the United States.² Renal parenchyma (renal cell) cancer accounts for about 85% of kidney cancers diagnosed in the United States from 1992 through 2002, while the remainder was composed mainly of renal pelvis cancer (approximately 12%) and other rare malignancies (approximately 2%).³ Virtually all renal cell cancers are adenocarcinomas, while the majority of cancers of the renal pelvis are transitional cell carcinomas. In this review for the most part we emphasize results for renal cell cancer because it is the predominant form of kidney cancer and it is increasing in incidence.

DEMOGRAPHIC PATTERNS

Renal cell cancer occurs about twice as often in men as in women.¹ Average age at diagnosis is in the early 60s (fig. 1). Incidence rates for renal cell cancer have been increasing steadily each year in Europe and the United States in the last 3 decades (fig. 2).⁴ This increase cannot be entirely accounted for by improved imaging modalities since an increasing incidence of late stage renal cell cancers has also been observed.^{4,5} Furthermore, rates have increased, although the number of unsuspected renal cell cancers de-

tected only at autopsy has decreased due to decreasing autopsy rates.⁶ Increases in incidence have been more rapid in females than males⁷ and in black than white individuals,⁵ leading to a substantial shift in excess from white to black individuals,⁵ which is becoming more pronounced with time. Age adjusted incidence rates of renal cell carcinoma in white men, white women, black men and black women in the United States during 1992 to 2002 were 13.8, 6.6, 16.8 and 8.0/100,000 person-years, respectively (table 1).

The incidence of cancer of the renal pelvis has decreased slightly in white men in the last 3 decades, while rates in white women and black individuals have remained relatively stable (data not shown).⁴ Age adjusted incidence rates in white men, white women, black men and black women in the United States during 1992 to 2002 were 1.66, 0.90, 1.18 and 0.68/100,000 person-years, respectively (table 1).

The prognosis in patients diagnosed with renal cell cancer has slowly improved with time with 5-year relative survival rates as high as 64% by 2002 compared with less than 40% in the early 1960s (table 2).⁵ A similar increase in 5-year relative survival has not been observed for cancer of the renal pelvis, for which rates are lower, particularly in women (table 2). However, relative survival is likely to underestimate the true survival rate for renal pelvis cancer since the average patients with renal pelvis cancer are heavy smokers who are also at high risk for many other causes of death. In fact, when calculating cause specific survival instead, ie the probability of a patient with kidney cancer dying with kidney cancer as the cause of death, the survival rates for renal cell and renal pelvis cancer are more

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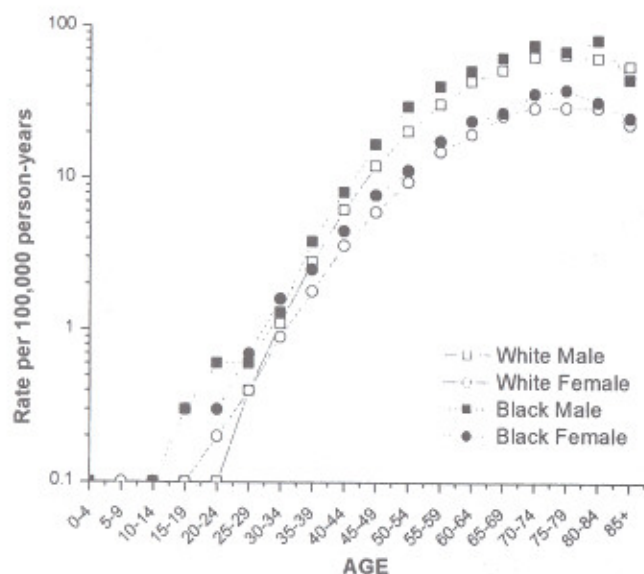


FIG. 1. Age specific incidence of renal cell cancer in United States by race and sex in 1992 to 2002 based on SEER data for 13 geographic regions of United States, including Atlanta, Georgia; Connecticut; Detroit, Michigan; Hawaii; Iowa; Los Angeles County, California; New Mexico; San Francisco/Oakland and San Jose/Monterey, California; Seattle/Puget Sound, Washington; Utah; rural Georgia; and Alaska natives.³

similar (table 2). In the United States and Europe kidney cancer mortality rates, which have not been partitioned by kidney subsite and are based on deaths from renal pelvis cancer along with those from cancer of the renal parenchyma, increased until the middle 1990s, after which the rates stabilized (fig. 3).⁸

Rates of renal cell cancer vary internationally more than 10-fold, suggesting a strong role for exogenous risk factors,

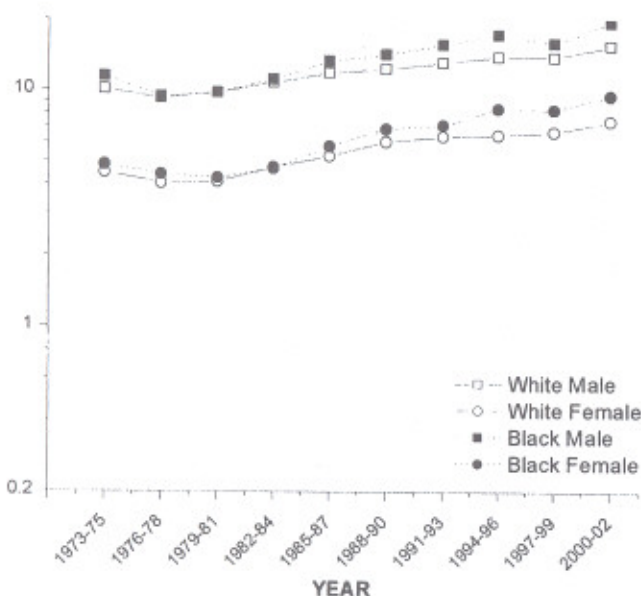


FIG. 2. Trends in 2000 United States standard age adjusted incidence of renal cell cancer by race and sex in 1973 to 2002 based on SEER data for 9 geographic regions of United States, including Atlanta, Georgia; Connecticut; Detroit, Michigan; Hawaii; Iowa; New Mexico; San Francisco/Oakland, California; Seattle/Puget Sound, Washington; and Utah.³

TABLE 1. Incidence rates* for renal parenchyma and renal pelvis cancer by racial/ethnic group and sex according to SEER program in 1992 to 2002³

	No. Males	(rate)	No. Females	(rate)
Renal parenchyma:				
White	18,489	13.77	10,908	6.60
Black	2,296	16.77	1,465	7.95
Asian	1,195	7.30	651	3.29
American Indian	212	14.66	133	7.33
White nonHispanic	16,384	13.79	9,568	6.56
White Hispanic	2,076	13.44	1,320	6.89
Renal pelvis:				
White	2,104	1.66	1,563	0.90
Black	150	1.18	118	0.68
Asian	164	1.13	103	0.56
American Indian	7	0.42	5	0.30
White nonHispanic	1,936	1.70	1,435	0.91
White Hispanic	165	1.37	123	0.74

* Per 100,000 person-years, age adjusted using 2000 United States standard.

in addition to possible roles of geographic differences in genetic susceptibility and diagnostic variability. The incidence is generally highest in several Western and Eastern European countries as well as in parts of Italy, in North America and in Australia/Zealand. The lowest rates are reported in Asia and Africa.¹

MATERIALS AND METHODS

Epidemiological studies for consideration in this review were identified through a MEDLINE® search of the literature. Our previously published review of the epidemiology of renal cell cancer included all studies published through 1999.⁹ For the purposes of this updated review all articles published from 1999 through 2006 were identified by the term renal cancer or the term kidney cancer together with the term risk factor or epidemiology. Moreover, all review articles addressing risk factors for kidney cancer in general or renal cell cancer in particular were identified and, if necessary, references were examined to supplement studies recovered through the initial search. Findings of individual studies were evaluated and a qualitative summary of the results is presented. In the interest of keeping our review to a reasonable length and within the limitations set by the Journal of Urology® we have not attempted to cite every

TABLE 2. Five-year relative and cause specific survival rates for renal parenchyma and renal pelvis cancer by race and sex according to SEER program in 1992 to 2002³

	% Males	% Females
Relative survival		
Renal parenchyma:		
Whites	64.2	64.8
Blacks	58.6	63.0
Renal pelvis:		
Whites	58.2	47.9
Blacks	61.3	48.1
Cause specific survival		
Renal parenchyma:		
Whites	65.9	67.8
Blacks	69.0	70.4
Renal pelvis:		
Whites	68.5	59.4
Blacks	69.0	72.0

Survival rates 5 years following diagnosis of first primary cancer in the renal parenchyma or renal pelvis.

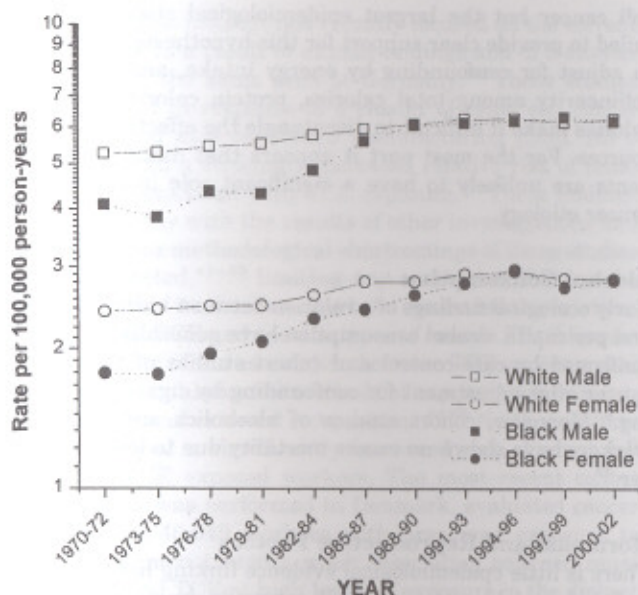


FIG. 3. Trends in 2000 standard age adjusted mortality from kidney cancer by race and sex in 1969 to 2002 based on National Center for Health Statistics data for entire United States.³

study that we identified. Rather, we emphasize findings that reflect consistency in the literature.

Virtually all information on risk factors for renal cell cancer comes from a large number of case-control studies performed in many countries, including the United States, Canada, England, Australia, Italy, Finland, France, Denmark, Sweden and China, although in the last few years the results of a number of cohort studies have been published. The largest and most comprehensive study to date, based on 1,732 cases and 2,309 controls, was a multicenter investigation performed in 5 countries using a common protocol, questionnaire and field procedures.¹⁰⁻¹⁷ Although groups at individual study centers participating in this international study have reported center specific results, throughout this review only the combined multicenter results are reported.

Renal cell cancer and renal pelvis cancer generally reflect different risk factor patterns. Since the overwhelming risk factor for renal pelvis cancer is cigarette smoking and in the past the abuse of analgesics containing phenacetin, we have limited the risk factor review to studies that focus specifically on renal cell cancer.

Renal cell cancer occurs in sporadic and familial forms. Having a first degree relative with kidney cancer has been associated with a 2 to 3-fold increased risk in most studies.¹⁸ Few cancers have as many different types of genetic predisposition as renal cell cancer, although to date only about 2% of renal cell cancer cases can be explained by genetic predisposition. Due to the extensive literature on genetics and renal cell cancer¹⁹⁻²¹ the area was not addressed in this review of exogenous risk factors.

RISK FACTORS

Socioeconomic Factors

The generally higher mortality and incidence rates for kidney cancer in urban than in rural areas¹ is apparent primarily in men. It probably reflects history of cigarette smoking as well as the greater availability of medical care and

imaging technology in urban than in rural areas. In general no consistent association has been demonstrated between renal cell cancer and social class variables, such as education or income.

Cigarette Smoking

Cigarette smoking is the most consistently established causal risk factor for renal cell cancer.⁹ It has been estimated to account for approximately 20% to 30% of renal cell cancers in men and 10% to 20% in women.^{9,10} A recent meta-analysis, which pooled data from 19 case-control studies based on 8,032 cases and 13,800 controls, and 5 cohort studies based on 1,457,754 participants with 1,326 renal cell cancer cases, revealed a relative risk of 1.54 and 1.22 in male and female smokers, respectively.²² There was a strong dose dependent increase in risk, with a relative risk of 2.03 in heavy male smokers and 1.58 in heavy female smokers with heavy smoking defined as 21 or more cigarettes daily. Renal cell cancer risk associated with cigarette smoking has been shown to decrease significantly with years of cessation in men and women, with a 15% to 30% decrease in risk after 10 to 15 years of quitting.²²

Obesity

Obesity has been linked to an excess risk of renal cell cancer in virtually every case-control and cohort study that has examined this relation. A few early studies showed the association primarily in women but most studies have demonstrated an effect of increased body mass index that is equally strong in men and women.^{17,23,24} A recent quantitative review of the published literature indicated a summary relative risk for renal cell cancer of 1.07/U increase in body mass index.²³ This estimate is remarkably consistent with that in a recent prospective study based on 2 million Norwegian men and women with standardized weight and height measurements.²⁴ In that study the relation between body mass index and renal cell cancer was more pronounced in those who never smoked.

The increasing prevalence of obesity may partly explain the increasing incidence of renal cell cancer. In fact, the proportion of renal cell cancers attributable to overweight and obesity is estimated to be more than 40% in the United States and more than 30% in Europe.^{23,25}

Obesity and hypertension are believed to act independently as renal cell cancer risk factors in men and women. Lipid peroxidation, which is increased in obese and hypertensive subjects, is hypothesized to be partly responsible for these associations through the formation of DNA adducts.²⁶ Obesity may act by promoting hormonal changes, such as increased peptide levels, and steroid hormones or increased insulin-like growth factor I associated with increasing body mass index in men and women could contribute to renal cell cancer.²⁵ Obesity may also predispose to a higher glomerular filtration rate and renal plasma flow independent of hypertension as well as to arteriosclerosis, which may in turn render the kidney more susceptible to carcinogenesis.

Hypertension and Antihypertensive Drugs

It is difficult to separate the influences on renal cell cancer risk of hypertension and its treatment with antihypertensive medications. Moreover, early stage, prediagnostic renal

tumors may themselves lead to increased blood pressure. A recent study showed an increasing prevalence of hypertension in the United States, particularly in black individuals and in women,²⁷ which may explain in part the recent trends of increasing renal cell cancer incidence.

The weight of the epidemiological evidence suggests that it is hypertension, rather than diuretics or other antihypertensive drugs, that influences the development of renal cell cancer. Most but not all studies have demonstrated an increased risk of renal cell cancer even after excluding the first 5 or 10 years before diagnosis, when preclinical disease or undetected renal cell cancers may cause increased blood pressure, rather than the reverse.⁹

The mechanism by which high blood pressure may affect renal cell cancer risk is unclear. However, hypertension induced renal injury may have a role or hypertension may be associated with metabolic or functional changes in the renal tubules that increase susceptibility to carcinogens. The hypothesis that renal cell cancer is more likely to be diagnosed incidentally in patients being treated for hypertension was not supported by a recent analysis.²⁸

Animal studies have linked the commonly used diuretics hydrochlorothiazide and furosemide with kidney tumors in rats.⁹ Moreover, these compounds act on the renal tubules, which are the site of origin of renal cell cancers. Most recent epidemiological studies suggest that diuretic use is not an independent risk factor for renal cell cancer since adjustment for high blood pressure appears to eliminate any excess risk associated with diuretic use.^{11,29} No particular class of other antihypertensive medications has been consistently associated with renal cell cancer risk.³⁰

Analgesics

Historically an association between chronic heavy use and abuse of phenacetin containing analgesics and transitional cell cancers of the renal pelvis has been clearly established but their effect on adenocarcinomas of the renal parenchyma is less conclusive.⁹ Any association with renal cell cancer is now difficult to assess because phenacetin containing analgesics have been off the market for at least 25 years in most countries and reliable recall of past intake is no longer practical.

With respect to other types of analgesics, most studies have focused on acetaminophen, which is the major metabolite of phenacetin, although several have also presented data on aspirin use. Neither acetaminophen, aspirin nor other types of nonsteroidal anti-inflammatory drugs have been convincingly linked with renal cell cancer. The large, international population based, case-control study showed no link with acetaminophen or aspirin use.¹² Moreover, no consistently increasing risks were observed with increasing consumption. The results of a large study in the United States designed to evaluate this association failed to show any link with regular use or duration of use of acetaminophen.³¹

Diet

Except for the relatively consistent protective effect of fruit and vegetable consumption,³² convincing evidence linking specific dietary factors and renal cell cancer risk has not been reported. Some epidemiological studies suggest that increased protein consumption may be a risk factor for renal

cell cancer but the largest epidemiological study to date failed to provide clear support for this hypothesis.¹⁷ Failure to adjust for confounding by energy intake, and the high collinearity among total calories, protein calories and fat calories make it difficult to disentangle the effects of calorie sources. For the most part it appears that dietary components are unlikely to have a significant role in renal cell cancer etiology.

Alcohol Consumption

Early ecological findings of a relation between kidney cancer and per capita alcohol consumption have generally not been confirmed by case-control and cohort studies of renal cell cancer after adjustment for confounding by cigarette smoking.⁹ Moreover, cohort studies of alcoholics and brewery workers have shown no excess mortality due to kidney cancer.³³

Hormonal and Reproductive Factors

There is little epidemiological evidence linking hormone associated variables to renal cell cancer in humans. In the large, international case-control study a significantly decreased risk was associated with the use of oral contraceptives but it was restricted to women who did not smoke,¹⁵ while another study showed no such relationship.³⁴ Similarly the association between prior hysterectomy or oophorectomy and the risk of renal cell cancer has been inconsistently reported.^{15,34}

Occupation

Renal cell cancer is not generally considered an occupationally associated tumor.⁹ However, numerous epidemiological studies have been performed during the last 3 decades that included queries on occupation and a number of sporadic associations have been reported between exposure or jobs/industries and renal cell cancer. Asbestos was linked to kidney cancer in 2 cohort studies, including 1 of insulators and 1 of asbestos product workers.⁹ A positive association between self-reported asbestos exposure and renal cell cancer was reported in several other case-control studies, including a large international study that included 200 exposed cases and showed a moderate relative risk of 1.4 with self-reported asbestos exposure.¹⁴ However, data on the duration of exposure did not support an association. An extensive meta-analysis of occupationally exposed cohorts indicated little association between kidney cancer risk and asbestos exposure.³⁵

In the early 1980s gasoline was suspected as a risk factor for renal cell cancer when male rats exposed in the long term to unleaded gasoline vapors developed a significant excess of renal cancers. Since then, a number of epidemiological studies have examined the effect of gasoline exposure and the collective evidence to date does not support a relationship between gasoline and the risk of renal cell cancer.³⁶ No association with gasoline was observed in numerous occupational cohort and nested case-control studies performed in different exposed worker populations,^{37,38} and a recent mortality and cancer morbidity study in a cohort of Canadian petroleum workers did not indicate an excess of kidney cancers.³⁹ Finally, the bioassay finding in male rats was due to a unique sex and species related compound α 2-microglobulin, which is unlikely to be relevant to humans.³⁶

Considerable interest has recently focused on the solvent TCE, largely as a result of animal findings and of 3 studies performed in the same area of Germany.⁴⁰ These studies were initiated in response to a cluster of renal cell cancer cases reported at a cardboard manufacturing plant. All 3 studies showed a strikingly increased relative risk of renal cell cancer associated with TCE exposure.⁴⁰ These findings contrast starkly with the results of other investigations and several serious methodological shortcomings of these studies have been noted,⁴¹⁻⁴³ limiting any conclusion that can be drawn. To date 7 cohort studies have evaluated the relationship between TCE and specific types of cancer. The 2 largest studies to date of the association between TCE exposure and cancer used sophisticated methods of exposure assessment, and internal and external comparisons.^{44,45} Neither of these studies showed a significantly increased risk of renal cell cancer in TCE exposed workers. The most recent cohort study, which was performed in Denmark, evaluated cancer morbidity in 40,049 workers with presumed exposure to TCE.⁴⁶ It demonstrated a weak association between renal cell cancer and TCE at high levels of exposure in the distant past. However, the weight of the evidence to date does not provide consistent, credible support for the hypothesis that TCE is a cause of renal cell cancer in humans.

Kidney Transplantation and Dialysis

Patients undergoing long-term renal dialysis experience a substantially higher average annual incidence of renal cell carcinoma than the general population⁴⁷ and the risk appears to increase with increasing duration of dialysis. Acquired renal cystic disease of the native kidneys is believed to be the major risk factor for renal cell carcinoma in patients on dialysis independent of patient age or underlying renal disease.⁴⁸ Several recent studies of cancer risk subsequent to kidney transplantation showed a substantially increased risk of acquired renal cystic disease and renal cell cancer compared with that in the general population.⁴⁹

Radiation

Ionizing radiation appears to weakly increase the risk of renal cell cancer in patients treated for ankylosing spondylitis and cervical cancer. An increased risk was also observed in patients receiving radium 224 for bone tuberculosis and ankylosing spondylitis.⁹

CONCLUSIONS

A further reduction in cigarette smoking and a decrease in the rates of obesity and probably hypertension would likely curb to some degree the increasing incidence of renal cell cancer. Focused analytic epidemiological studies, including the evaluation of gene-environment interactions, are needed to specifically identify reasons for the increasing incidence in the last 25 years since a large proportion of renal cell cancers are not accounted for by risk factors, including cigarette smoking, obesity and hypertension. Particular attention should be focused on black Americans because their incidence rate has increased in the last 3 decades to significantly surpass that of white Americans. The roles of hypertension, obesity and genetics in this and other high risk populations should be thoroughly evaluated.

Abbreviations and Acronyms

SEER	=	Surveillance, Epidemiology, and End Results
TCE	=	trichloroethylene

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