Exhibit 215

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Risk Factors in Renal Cell Carcinoma. II. Medical History, Occupation, Multivariate Analysis, and Conclusions

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ABSTRACT Potential risk factors in renal cell carcinoma (RCC) were studied in a case-control study of 315 RCC cases and 313 hospital and 336 population controls. Risk factors included medical history, radiation exposure, predominant lifetime occupation, exposure to high-risk industries, and summary of important risk factors by a linear logistic regression model based on the comparison of RCC cases and controls selected from hospitals and the general population for 33 variables. A significant increase in urologic, cardiovascular, malignant, digestive, and metabolic disease was observed among cases over population controls. Exposure to radiation increased the risk, especially in females. A predominant lifetime occupation as a professional decreased the risk, whereas work as an operative increased the risk significantly. Work in petroleum-related and dry-cleaning industries were associated with elevated risk. Multivariate analysis comparing cases with each of the control groups for males and females identified obesity as the most important risk factor in RCC. Weight control at an early age might help to prevent the occurrence of a significant proportion of this rare but increasing malignant disease.

Key words: case-control study, radiation exposure, petroleum

INTRODUCTION

Renal cell carcinoma (RCC), the predominant lesion of kidney cancer [1], has shown a steadily increasing trend over time during the last several decades in both incidence and mortality, the rate of increase being affected by the sex/race group and/or the incidence/mortality measures used [2]. Among the handful of published case-control studies [3–9] only two [7,9] used multivariate analysis to examine the role of risk factors in the etiology of RCC. To clarify further the role of medical and occupational factors individually and simultaneously in the presence of other known or unknown risk factors, an ongoing population-based case-control study was undertaken using both univariate and multivariate analyses.

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MATERIALS AND METHODS

Individuals studied included 315 RCC cases and 313 hospital and 336 population controls. The methodology employed in selecting the cases and each of the control groups as well as the approach used to gather and analyze demographic, tobacco, beverage, and obesity data were described previously [10]. The univariate analysis in this study is limited to data on medical history, occupation, and radiation. Medical history was obtained by asking specific questions on the administered questionnaire about medical conditions the individual might have had in the past or might have at the time of the interview. Excluded were any conditions the individuals may have had during the 3 years preceding the interview. A number of these conditions were combined into broader medical groupings for the purpose of analysis. A history of congenital polymastia was ascertained by asking for the presence of circles of dark coloration on the chest other than the two primary nipples that are at least one-quarter inch across. No examination was performed to verify the presence of this condition. Hormone history was obtained by asking questions about regular hormone use for 3 months or more, excluding the 3 years preceding the date of the interview. Medication history was obtained by ascertaining the type of medication used for 1 month or longer, age at which medication was started, and duration of exposure to that medication. Individuals were asked about the kinds of pain relievers used 10 times or more during adult life, excluding the past 3 years preceding the interview. Duration of use information was also obtained. Radiation exposure was determined by asking if the individual had ever undergone any diagnostic radiologic tests for bladder or kidney conditions or had ever received radiation therapy to relieve medical conditions. The predominant occupation was determined by asking each subject what job he had held for at least 1 year and then determining which job was held the longest. Information on industrial exposure was elicited from each subject. An individual was classified as exposed to a certain substance if the exposure took place for a period of 1 year or longer. Specific petroleum-related occupations were determined from the lifetime occupational histories obtained from each subject.

The multivariate analysis employed Cox's linear logistic regression model [11–13]. The Biomedical Computer Program (BMDP) was used to perform the analysis. Both the forward and backward selection procedures were used in the linear logistic regression analysis. The multiple logistic model for matched case-control studies proposed by Breslow et al. [12,14] was used to obtain point estimates and 95% confidence limits of the odds ratios associated with exposure variables for hospital controls. The PECAN developed by Lubin [15] was used to perform the analysis.

RESULTS

History of Disease 3 Years Prior to Interview

Odds ratios (ORs) for RCC for history of disease are given in Table I. These data were arrived at by combining a number of disease entities. For males, elevated ORs are reported for histories of cancer, metabolic, nervous system, circulatory, and genitourinary diseases. The first three disease categories appear to be related to RCC risk with borderline significance, while the last two are associated in a very significant way (circulatory disease, OR = 1.5, confidence interval (C.I.) = 1.0–2.2; and genitourinary disease, OR = 1.6, C.I. = 1.1–2.5). In females, histories of metabolic diseases and benign tumors appear to be associated with RCC risk with borderline significance. A history of digestive disease is associated in a statistically significant way (OR = 1.9, C.I. = 1.1–3.5).

Of all the matched-pair comparisons betwen cases and hospital controls for diseases that were self-reported as diagnosed 3 years prior to the date of interview, none of the results were remarkable or of statistically significant importance except the value for males for whom a history of digestive diseases appears to be associated with RCC risk in a negative way (OR = 0.4, C.I. = 0.2–0.7).

TABLE I. Odds Ratios for Renal Cell Carcinoma for All Diseases

	Male				Female			
Disease[1]	Case	Control	OR[2]	95% C.I.	Case	Control	OR[2]	95% C.I.
Virus	198	190	0.5	0.2–1.4	103	137	0.5	0.1–2.8
Infection	150	128	1.2	0.8–1.4	78	108	0.7	0.4–1.3
Cancer	71	50	1.5*	0.9–2.3	30	32	1.3	0.7–2.4
Benign tumors	9	5	1.3	0.5–3.7	43	41	1.6	0.9–2.8
Metabolic	25	11	1.8	0.9–3.7	32	25	1.7	0.9–3.1
Nervous system	53	37	1.5	0.9–2.4	38	41	1.4	0.8–2.4
Circulatory	127	95	1.5*	1.0–2.2	71	84	1.1	0.7–2.0
Respiratory	105	105	0.9	0.6–1.3	60	79	1.0	0.6–1.6
Digestive	37	33	1.0	0.6–1.7	36	27	1.9**	1.1–3.5
Gen.-Urin.	80	52	1.6***	1.1–2.5	64	81	1.1	0.7–1.9
Skin	11	13	1.0	0.4–2.4	0	1	1.0	0.1–6.4
Muscle	19	14	1.3	0.6–2.7	10	6	2.2	0.8–5.9
Other	7	10	0.7	0.3–1.7	0	5	0.4	0.1–2.1
Injury	45	51	0.8	0.5–1.3	10	9	1.5	0.5–3.9
Accident	6	2	2.0	0.6–7.6	0	1	1.0	0.1–6.5

[1]Diseases were diagnosed 3 years prior to date of interview.
[2]Adjusted for age and weight.
*$P < 0.1$.
**$P = 0.0341$.
***$P = 0.0283$.

The association between RCC and histories of specific disease entities was examined. A number of the ORs appear to be elevated, but none reached the level of statistical significance. In males, a positive association is noted for history of kidney stones (OR = 1.6), kidney cysts (OR = 2.0), kidney injuries (OR = 2.1), prostate cancer (OR = 2.4), testicular cysts (OR = 1.4), and prostatitis (OR = 1.4). In females, associations were found betwen RCC and kidney stones (OR = 1.3) and between RCC and bladder infection (OR = 1.5).

Odds ratios for RCC and a history of cardiovascular diseases were generated. In males, the ORs are elevated for three of the variables; in two of these the association is of borderline significance, and in one it is statistically significant. A history of hypertension is positively and significantly associated with RCC risk (OR = 1.6, C.I. = 1.0–2.6). Likewise, a history of diabetes mellitus increases RCC risk twofold (OR = 2.2, C.I. = 0.9–5.1) and a self-reported history of fast heart beat increases the risk by 1.9 (C.I. = 0.9–4.2).

The results of the matched-pair analysis reveal values that are consistent with the case-population control comparisons. In males, histories of arthritis, hypertension, and kidney injuries are associated with increased RCC risk. The results of arthritis and hypertension are of borderline significance (arthritis, OR = 1.4, C.I. = 0.9–2.2; hypertension, OR = 1.4, C.I. = 0.9–2.1) but are statistically significant for kidney injuries (OR = 4.0, C.I. = 1.1–18.0). In females, the ORs for histories of kidney stones (OR = 4.5), kidney injuries (OR = 2.0), high cholesterol levels (OR = 1.4), and goiter (OR = 2.7) are elevated.

History of Polymastia

The association between RCC and polymastia was examined. There were only six cases, four males and two females. Polymastia was self-reported by two male population controls and by one male hospital control. Clearly more cases than either of the control groups reported congenital polymastia, but the small numbers make it difficult to draw any meaningful conclusions.

TABLE II. Odds Ratios (OR) for Renal Cell Carcinoma for Exposure to Diagnostic and Therapeutic Radiation

	Male				Female			
Radiation	Case	Control	OR[1]	95% C.I.	Case	Control	OR[2]	95% C.I.
Diagnostic for kidney or bladder	23	15	1.3	0.6–2.8	13	9	2.0	0.9–4.8
Any therapy	19	11	1.3	0.6–2.9	20	9	2.9*	1.3–6.4

[1]Adjusted for age, weight, and education.
[2]Adjusted for age and weight.
*$P = 0.01$.

History of Hormone, Medication, and Pain Reliever Use

The questionnaire contained self-reported data on hormone, medication, and pain reliever use. These results were analyzed. The numbers are extremely small; thus meaningful comparisons and interpretations cannot be made. In females, use of thyroid hormone doubles the risk for RCC and the OR = 2.1; this value is of borderline significance. The only other finding that is worthy of note is the weak positive association found between RCC and use of estrogen to alleviate menopausal symptoms. The values of the ORs for the independent and matched-pair analyses are on the order of 1.3 and 1.4, respectively.

Use of other medications for the treatment of a number of diseases reflects the association between RCC and these disease. For males, a number of the ORs are elevated and are either statistically significant or of borderline significance. They include insulin use (OR = 3.3, C.I. = 0.9–12.3), cardiovascular medication (OR = 1.7, C.I. = 1.0–2.8), electrolytes (OR = 1.7, C.I. = 0.9–3.2), and medications used for the treatment of hypertension (OR = 2.6, C.I. = 1.3–5.3). None of the results for the male data are striking considering the small numbers involved. However, the elevated ORs for the medications used to treat hypertension and other cardiovascular diseases are consistent with the results of the independent analysis.

There is also evidence of a negative association between sex hormone use in males and RCC risk (OR = 0.5, C.I. = 0.2–1.0).

Use of 29 different pain relievers was compared between cases and population controls and hospital controls. The independent analysis between cases and population controls showed a statistically significant association with use of Anacin (OR = 1.5, C.I. = 1.0–2.3) and Bufferin (OR = 1.7, C.I. = 1.1–2.7) in men and Darvon in women (OR = 3.5, C.I. = 1.7–7.2).

History of Radiation Exposure

Results of diagnostic radiation exposure for kidney or bladder disease and any lifetime radiation thereapy received are presented in Table II. All of the ORs are elevated, reaching statistical significance for females who received radiation therapy (OR = 2.9, C.I. = 1.3–6.4).

Occupation and High-Risk Industries

Odds ratios for RCC for predominant lifetime occupation for males are presented in Table III. It is worth noting that a number of occupational groups show some association with RCC risk. The professional group is negatively associated with the disease in a significant way. Likewise the clerical and operatives groups show about a twofold elevation in risk,

TABLE III. Odds Ratios for Renal Cell Carcinoma for Predominant Lifetime Occupations for Males

Occupation	Case	Control	OR[1]	95% C.I.
Professional	20	36	0.5*	0.3–1.0
Manager	16	19	0.8	0.4–1.6
Sales	9	8	1.1	0.4–3.0
Clerical	15	9	1.8	0.7–4.4
Crafts	44	44	1.0	0.6–1.7
Operatives	42	20	2.0**	1.1–3.5
Service	11	14	0.8	0.3–2.2
Laborer	12	7	1.4	0.5–3.5
Farmer	30	26	1.0	0.5–1.9

[1]Adjusted for age, smoking, and weight.
*$P = 0.035$.
**$P = 0.0188$.

TABLE IV. Odds Ratios for Renal Cell Carcinoma for High-Risk Industries

Industry/sex	Sex	Case	Control	OR[1]	95% C.I.
Chemical manufacturing	Males	8	3	1.9[2](3.3)	0.6–5.8
Machining	Males	13	7	1.7[2](2.1)	0.7–4.3
Painting/paint manufac.	Males	22	16	1.3	0.7–2.6
Petroleum refining	Males	31	5	4.3[2*](7.2)	1.7–10.9
and distributing	Females	4	2	1.6[2]	0.4–6.5
Welding	Males	29	22	1.2	0.7–2.2
Dry cleaning	Males	3	6	0.7[2]	0.2–2.3
	Females	8	1	2.8[2**](7.8)	0.8–9.8
Metal degreasing/					
cleaning	Males	19	10	1.7[2](1.9)	0.7–3.8

[1]Adjusted for age. ORs in parentheses are the Mantel-Haenszel values.
[2]Adjusted for age, smoking, and weight.
*$\chi^2 = 14.71$, $P = 0.0001$.
**$\chi^2 = 4.7$, $P = <0.03$.

reaching statistical significance for operatives at OR = 2.0 and C.I. = 1.1–3.5. The data were adjusted for age, smoking, and relative weight.

Similar results are found for males when cases are compared with hospital controls. The unique exception is a statistically significant finding for the farmers group (OR = 2.0, C.I. = 1.0–4.2). The results for the operatives group is slightly elevated in the positive direction but is not statistically significant. The results for the female occupational groups show an inverse association with the professional group and a positive association for craft and service worker groups. These results are of borderline significance.

Results from the industrial checklist (Table IV) show positive links with a number of industries, including chemical manufacturing (male OR = 1.9, C.I. = 0.6–5.8), machining (male OR = 1.7, C.I. = 0.7–4.3), petroleum refining and distributing (male OR = 4.3, C.I. = 1.7–10.9; female OR = 1.6, C.I. = 0.4–6.5), dry cleaning (female OR = 2.8, C.I. = 0.8–9.8), and metal degreasing/cleaning (male OR = 1.7, C.I. = 0.7–3.8). The Mantel-Haenszel ORs for all of these high-risk industries are slightly higher than the Woolf ORs, and in two instances they are substantially higher (petroleum refining/distributing and dry cleaning). The results of the matched-pair analysis of the case-hospital control comparisons are similar, but none reached statistical significance.

TABLE V. Summary of Important Risk Factors by Linear Logistic Regression Model Based on the Comparison of Renal Cell Carcinoma Cases and Population Controls for 33 Variables for Males

No.	Variable	Coefficient (β)	Standard error	*P* value	Adjusted OR	95% C.I.
1	Recent weight	0.680	0.163	0.0001	2.0	1.4–2.7
2	Petroleum work	1.882	0.546	0.0006	6.6	2.3–19.2
3	Hypertension	0.539	0.265	0.0414	1.7	1.0–2.9
4	Kidney stones	0.831	0.402	0.0385	2.3	1.0–5.0
5	Sweetener use	0.744	0.299	0.0128	2.1	1.2–3.8
6	Education years	−0.068	0.036	0.0574	0.9	0.87–1.0
7	Cancer history	0.629	0.281	0.0251	1.9	1.1–3.3
8	Wine use	−0.482	0.256	0.0588	0.6	0.4–1.0
9	Fast heart beat	1.116	0.599	0.0615	3.1	0.9–9.9
10	Arthritis	−0.523	0.270	0.0524	0.6	0.3–1.0
11	Smoking	0.520	0.300	0.0836	1.7	0.9–3.0

Other variables considered in the model include weight at age 20; total alcohol consumption; service, clerical operative, farming, professional, or dry-cleaning occupations; age; use of snuff; coffee consumption; bladder infection; diabetes; G-U disease; sex hormone, hormone, and thyroid hormone use; kidney injury; metabolic disease; GI disease; benign tumor; and hard liquor consumption.

Multivariate Analysis

The data were analyzed separately for males and females. Because of the large number of variables, only those variables that were statistically significant in the univariate analysis in any of the subgroups, or were mentioned in the literature, or were thought to be potential confounders were included in the regression models. Subsequently, the number of variables entered into the models was more manageable.

In Table V we present the results of Cox linear logistic regression analyses with cases and population controls for males. When 33 variables were entered into the model, only 11 of them showed a statistically significant association with risk of RCC. In five of these variables the *P* values were between the 0.05 and 0.10, and the 95% C.I. were of borderline significance. The six most important risk factors in males for RCC, listed by relative importance, are recent weight (OR = 2.0, C.I. = 1.4–2.7), work in a petroleum-related industry (OR = 6.6, C.I. = 2.3–19.2), history of hypertension (OR = 1.7, C.I. = 1.0–2.9), history of kidney stones (OR = 2.3, C.I. = 1.0–5.0), use of artificial sweeteners (OR = 2.1, C.I. = 1.2–3.8), and personal history of cancer (OR = 1.9, C.I. = 1.1–3.3). Three of the five variables with associations of borderline significance are inversely related to risk of RCC, and they include years of education attained, ever use of wine, and history of arthritis. There were also weak positive associations between RCC risk and a self-reported fast heart beat and a history of smoking. These significant findings from the multivariate analysis are consistent with those previously reported for the univariate analysis of the male data for case-population control comparisons.

Similar results were obtained for males when the total number of variables entered into the model was reduced from 33 to 15. There was a change in the rank order of the relative importance of the variables on risk. For instance, genitourinary disease replaced kidney stones in importance and appeared as the third most important risk factor. Hypertension moved from third to fourth, wine use moved up to five and became more significant, and diabetes mellitus was sixth, with OR = 3.0 and C.I. = 1.0–9.0. Fast heart beat moved up to seventh, followed by history of cancer, weight at age 20, and the operative occupational group. The change in rank order may be due to the change in the number of patients (with complete data on all variables) used in the model. The results of the case-population control analysis for females are

TABLE VI. Summary of Important Risk Factors by Linear Logistic Regression Model Based on the Comparison of Renal Cell Carcinoma Cases and Population Controls for 33 Variables for Females

No.	Variable	Coefficient (β)	Standard error	*P* value	Adjusted OR	95% C.I.
1	Weight at age 20	0.791	0.266	0.003	2.2	1.3–3.7
2	GI illness	0.681	0.344	0.048	2.0	1.0–3.9
3	Occup. operators	−2.441	1.142	0.032	0.09	0.01–0.8
4	Benign tumors	0.673	0.320	0.036	2.0	1.0–3.7
5	Occup. dry cleaners	2.160	1.142	0.059	8.7	0.9–81.3
6	Education years	−0.107	0.049	0.030	0.9	0.8–1.0
7	Bladder infection	0.546	0.325	0.094	1.7	0.9–3.3

Other variables considered in the model include recent weight; total alcohol consumption; service, clerical, professional, and farming occupations; smoking; snuff use; coffee consumption; kidney stones; oil work; hypertension; cancer; fast heart beat; age; diabetes; G-U disease; sex hormone, hormone, and thyroid hormone use; arthritis; wine consumption; kidney injuries; metabolic disease; use of artificial sweeteners; and hard liquor consumption.

TABLE VII. Summary of Important Risk Factors by Linear Logistic Regression Model Based on the Comparison of Renal Cell Carcinoma Cases and Hospital Controls for 30 Variables for Males

No.	Variable	Coefficient (β)	Standard error	*P* value	Adjusted OR	95% C.I.
1	Snuff use	1.664	0.639	0.009	5.3	1.5–18.5
2	G-U illness	0.915	0.394	0.021	2.5	1.2–5.4
3	Arthritis	0.413	0.246	0.093	1.5	0.9–2.4
4	Thyroid hormone use	−2.141	1.249	0.086	0.1	0.01–1.4
5	GI illness	−0.883	0.327	0.007	0.4	0.2–0.8

Other variables in the model include weight, recent and at age 20; farming, dry cleaning, professional, and operator occupations; hormone and sex hormone use; kidney infection; hypertension; smoking; age; coffee and sweetener consumption; tumors; kidney stones; education; alcohol consumption; petroleum work; cancer; fast heart beat; diabetes; wine consumption; metabolic disease; and bladder infection.

in Table VI. When the total number of variables entered into the model is 33, seven of these were statistically significant or of borderline significance. Weight at age 20 appeared to be the most important risk factor in females (OR = 2.2, C.I. = 1.3–3.7), followed by history of gastrointestinal illness (OR = 2.0, C.I. = 1.0–3.9), the operators occupation group (OR = 0.09, C.I. = 0.01–0.08), history of benign tumors (OR = 2.0, C.I. = 1.0–3.7), exposure to dry-cleaning solvents (OR = 8.7, C.I. = 0.9–81.3), years of education attained (OR = 0.9, C.I. = 0.8–1.0), and bladder infections (OR = 1.7, C.I. = 0.9–3.3). It should be noted that the association between RCC and exposure to dry-cleaning solvents and bladder infection is of borderline significance. When only the 11 most important variables were entered into the model, weight at age 20 and a history of gastrointestinal disease retained their important ranking and exposure to dry-cleaning solvents emerged as a strong third, with OR = 9.4 and 95% C.I. = 1.1–82.2. History of metabolic disease became important but is of borderline significance as an etiologic risk factor. These data are consistent with the results of the univariate analysis presented earlier.

Tables VII and VIII present results of the case-hospital control comparison using the Cox model. Table VII shows that snuff use, followed by genitourinary illness, history of arthritis, use of thyroid hormones, and a history of gastrointestinal illness are the five factors for RCC

TABLE VIII. Summary of Important Risk Factors by Linear Logistic Regression Model Based on the Comparison of Renal Cell Carcinoma Cases and Hospital Controls for 29 Variables for Females

No.	Variable	Coefficient (β)	Standard error	*P* value	Adjusted OR	95% C.I.
1	Recent weight	0.333	0.193	0.084	1.4	1.0–2.0
2	Weight at age 20	0.275	0.287	0.342	1.3	0.7–2.3
3	Sex hormone use	2.206	1.199	0.066	9.1	0.9–95.3
4	Coffee consumption	1.833	0.703	0.009	6.3	1.5–24.8
5	Clerical occupation	1.115	0.649	0.085	3.1	0.9–10.9
6	Bladder infection	−0.787	0.439	0.073	0.5	0.2–1.1

Other variables considered in the model include farming, professional, dry cleaning, and service occupations; hormone use; history of arthritis; history of tumors; GI illness; kidney infection; hypertension; smoking; snuff use; sweetener use; kidney stones; alcohol and wine consumption; history of cancer; fast heart beat; history of diabetes; metabolic disease; G-U disease; and education.

for males when cases are compared with hospital controls. For the female population (Table VIII), the most important risk factors are recent weight (OR = 1.4, C.I. = 1.0–2.0), weight at age 20 (OR = 1.3, C.I. = 0.7–2.3), use of sex hormones (OR = 9.1, C.I. = 0.9–95.3) and use of coffee (OR = 6.3, C.I. = 1.6–24.8). The clerk occupation group is of borderline significance.

DISCUSSION

Associated Diseases

A number of studies of different types of clinical, observational, and autopsy series have reported on the association between various diseases and RCC. The association with diabetes mellitus came exclusively from two autopsy studies [16,17]. These two studies lacked controls and strict diagnostic criteria. It is worth noting that Kessler [18] found no relationship with RCC when he investigated the mortality among 21,447 registered diabetics in Boston. Studies of hypertensive populations have documented association with RCC [19–21].

Renal cell carcinoma has been associated with von Hippel-Lindau disease. Nearly two-thirds of these patients have RCC [22]. Wynder et al. [5] found that a significantly greater percentage of cases of RCC (7%) had a history of myocardial infarction than did controls (1%). Holland and Frei [23] found hypercholesterolemia to be associated with kidney cancer.

The positive association found with circulatory disease, digestive disease, hypertension, and diabetes mellitus is linked to obesity. High fat intake, hormonal imbalance and arteriolonephrosclerosis could be factors in making the kidney more susceptible to cancer.

Hormones

The effect of hormones deserves investigation. Bloom [24] cited evidence that RCC is hormone–dependent. Wynder et al. [5] reported on several animal experiments in which a variety of estrogens were used to induce renal tumors in male and female hamsters. In a survey of the use of estrogens during pregnancy in the United Kingdom no evidence was found of an elevated incidence or mortality from kidney cancer [25]. These results should not be interpreted as conclusive because the follow-up period was short.

Our results show a weak positive association with the use of estrogen to alleviate menopausal symptoms. This is the only finding in all the hormone data that is positive and consistent, and the numbers are large enough for correct interpretation. The idea of Wynder et al. [5] that RCC is a hormone-dependent tumor was based on their finding that obesity was associated with RCC in females only. Our results of a positive association between RCC and obesity in both men and women and the weak positive association with estrogen use make the

hormone-dependent hypothesis less attractive. More studies should be carried out in this area to determine what role is played by hormones in the etiology of RCC, if any.

There are a number of reports implicating prolonged administration of estrogens in the production of renal adenomas and RCC in the male Syrian gold hamster and in European hamsters [26,27]. The association between estrogen use and RCC in humans is not clear at this time. Bellet and Squitieri [28] and Nissenkorn et al. [29] reported RCC in a total of three patients who were treated for prostatic cancer with estrogens. It is noteworthy that 10 RCC patients in the present study had a history of prostatic cancer.

Other Medications

The association of medication usage with RCC reflects on the significance of certain diseases such as hypertension, diabetes, and cardiovascular disease. The medications themselves are not believed to be the important factors.

Analgesics

Of all the analgesics examined in our study, only three were positively associated with RCC risk in a significant way. These were Darvon, Anacin, and Bufferin. The association with Darvon is the most impressive and consistent of the three.

Armstrong et al. [30] reported a statistically significant ($P < 0.005$) association between RCC and those persons taking analgesics daily. However, they discounted their finding as being causal because 6 of 15 users had taken them for less than 1 year. It is interesting that the majority of the analgesics in their study did not contain phenacetin, which has been implicated in cancer of the renal pelvis [31–33]. Since Darvon, Anacin, and Bufferin do not contain phenacetin, the significant association may be caused by the medical conditions for which they are taken.

Radiation

There is ample evidence from both human and animal studies that suggests an increased susceptibility of the kidney to radiation exposure. It has been possible to produce experimentally both benign and malignant tumors of the kidney in rats and mice by whole or partial X-, neutron, and gamma radiation [26]. Thorium dioxide (Thorotrast), an α-emitting contrast medium used decades ago in procedures such as retrograde pyelography, has been reported by a number of investigators [34–36] to cause kidney tumors in humans. Many of these tumors, however, were in the renal pelvis [37,38]. Smith and Doll [39], in a recent study on X-ray treatment of patients with ankylosing spondylitis, reported a twofold increase of kidney cancer. Thus, the association found in our study for diagnostic and therapeutic radiation is consistent with previously published reports in animals and humans. The fact that the association in men is positive but weak and the association in women is strong and significant, especially for any radiation therapy, may be explained by the common use of radiation therapy for cancers of the cervix, endometrium, and ovary.

Occupation

Several studies have reported an elevated kidney cancer risk in various occupational groups. These groups include coke oven workers in steel plants; lead-, asbestos-, and cadmium-exposed workers; lumberjacks; pressmen; dry cleaners; petroleum workers; professionals; trade industry workers; electricians; and electrical and sale workers.

Coke oven workers in 12 steel plants in the United States and Canada were studied by Redmond et al. [40] and were found to have a highly significant 7.5-fold increase in risk of dying from kidney cancer. The risk estimate was based on eight kidney cancer deaths, one of which was reported to be a transitional cell cancer of the renal pelvis. In Great Britian, coke oven workers were found to have excessive mortality from kidney cancer during a 1949–1953 study period, but this excess was not found in data covering the periods 1959–1963 and

1970–1972 [41,42]. Other occupational analyses of mortality data show an elevation in kidney cancer deaths in the iron and steel industries of the United States, which include coke oven workers [43–46].

Lead has been investigated extensively as a potential carcinogen. No association was found with kidney cancer in studies in the early 1950s and 1960s [47,48]; however, recent data by Berg and Burbank [49] show a statistically significant correlation between kidney cancer mortality and lead concentration in water systems in the United States.

Studies of asbestos-exposed populations in the United States and Canada by Selikoff et al. [50], Graham et al. [51], and Kanarek et al. [52] showed elevation in kidney cancer risk among asbestos and insulation workers, for women living in asbestos mining counties, and for women in the San Francisco Bay area exposed to high levels of asbestos in the drinking water.

Exposure to cadmium has been reported to increase kidney cancer risk in one case-control study [6] but not in other studies of humans and animals [53–57]. Three mortality studies of pressmen, printers, and workers exposed to dyes containing lead and cadmium have reported an elevation in mortality from kidney cancer among workers [58–60]. In Sweden, lumberjacks were reported in one case-control study [61] to have experienced high kidney cancer risk. In another study, Milham [60] reported an elevation in the proportionate mortality ratios for sawyers, sawmill workers, and sawfilers.

The most significant occupational evidence to date concerns the relationship between dry cleaning and kidney cancer. Several studies in a number of states and among union members have all reported a consistent elevation in kidney cancer risk. Duh and Asal [62] studied 440 deaths among Oklahomans who died between 1975 and 1981 and had worked in laundry and dry-cleaning establishments, and they observed seven kidney cancer deaths when less than two were expected. The standardized mortality odds ratio (SMOR) was 3.8 and the 95% C.I. was 1.9–7.6. Katz and Jowett [63] found seven kidney cancer deaths among 671 female dry cleaners when two deaths were expected. The PMR was 257 ($P = 0.05$). Blair et al. [64] conducted a mortality study among laundry and dry-cleaning workers in Saint Louis and Kansas City and found two deaths when one was expected. The PMR was 200 and the period of the study was 1957–1977. Brown and Kaplan [65] expanded and extended the union membership study of dry cleaners to 1960–1982 and reported a standardized mortality ratio (SMR) of 200 for kidney cancer. Two additional death certificate studies in the states of Washington [66] and Massachusetts [67] reported an elevation in kidney cancer risk in females (PMR = 145) and males (PMR = 466; $P = 0.01$), respectively.

These studies are limited because of relatively small numbers of deaths, relying on death certificate data to identify the population of interest (which occasionally combine the occupational codes for dry cleaners with launderers), and lack of data on specific solvent exposures and durations of exposure. Although not solvent specific, the findings in these studies were generally intepreted as being the possible effects of exposure to perchloroethylene. Considering the evolution in dry-cleaning solvent usage and the latent period in cancer, these changes in cause-specific mortality might be more accurately ascribed to exposures to petroleum dry-cleaning solvents.

A retrospective study by Bryan [68] of 197 renal cell carcinoma cases compared with controls showed male laundry and dry-cleaning workers to have a significantly elevated OR of 17 ($P = 0.05$), while female laundry and dry-cleaning workers had a nonsignificantly elevated OR of 4.32. The study was limited by the small number of individuals involved and by the fact that some of the data were provided by next-of-kin.

Recently, the discovery of renal tumors in male rats exposed to whole, unleaded gasoline vapors increased the interest in the relationship between renal cancer in workers exposed to petroleum products [69]. There are a number of surveys of petroleum refinery workers but with inconsistent results. Thomas et al. [70] studied the mortality of workers employed in petroleum refining and petrochemical plants in Texas between 1947 and 1977 and found seven deaths from kidney cancer when only 2.8 were expected among white men

exposed for 20 years or more. The PMR was 2.51 ($P = 0.05$). McLaughlin et al. [71] in a large case-control study in Minnesota found no overall association between renal cell cancer risk and work in the broad category of jobs with potential for exposure to petroleum products. However, an excess risk was noted among long-term workers who were nonsmokers and an increasing risk with duration of employment among gasoline station attendants. Weaver [72] summarized reviews of epidemiologic studies of causes of death in workers exposed to petroleum products. The cohort study by Rushton and Alderson [73] of eight refineries in Great Britian found 12 kidney cancers when only seven were expected. The SMR was 171, which was of borderline significance [73]. Additional studies of petroleum refinery workers by Hanis et al. [74,75] and by Wen et al. [76] have shown slight to moderate elevations in kidney cancer mortality risks whereas the studies of Rushton and Alderson [77], Kaplan [78], Devine et al. (unpublished data), Morgan and Wong [79], and Morgan [80] all have been negative.

The results of our investigation show that those persons whose predominant lifetime occupation places them in professional categories are at a low risk of acquiring RCC. The results obtained from the case-hospital and case-population control comparisons are consistent. Professionals are less likely to be exposed to toxic agents like hydrocarbons, which are widely prevalent in the work place and are normally associated with RCC risk.

The risk associated with male operatives is influenced by the high prevalence of truck drivers among the cases. Truck drivers are known to be exposed to numerous hydrocarbon compounds that can be harmful to the kidney. The elevated risk associated with farming is limited to the case-hospital control comparisons. The data are not consistent in this regard. One possible explanation is the high exposure of farmers to pesticides that are hydrocarbon derivatives. The elevated risk found with the female occupational group service workers only reflects the predominance of dry cleaners in cases compared with hospital controls and/or population controls. The results of the checklist of high-risk industries also revealed an increased risk for women in dry cleaning. The increased risk in both sexes associated with petroleum refining and distributing confirms findings of several studies of workers exposed to petroleum products discussed earlier. The occupational category of petroleum refining and distributing includes individuals who have worked in oil fields, in refineries, in oil distribution, and as gas station attendants, all of whom come into contact with petroleum products. The significant association found with gasoline attendants is consistent with the excess of kidney tumors found in male rats exposed to gasoline vapors. The positive association found among women dry cleaners confirms results obtained from several mortality studies and is consistent with the finding among petroleum workers in that the predominant solvent used in dry cleaning in Oklahoma historically has been Stoddard compound, a petroleum derivative.

SUMMARY AND CONCLUSIONS

Renal cell carcinoma (RCC) accounts for more than 85% of kidney cancer incidence and 2% of all cancer incidence in the United States. While its etiology remains obscure, a handful of epidemiologic studies have implicated cigarette smoking, certain occupational exposures, and obesity in women as risk factors. To clarify further the role of these and other factors, both genetic and environmental, an ongoing case-control study was undertaken.

Three hundred fifteen newly diagnosed and confirmed (95% by tissue, 5% by X-ray) cases were identified from 29 hospitals in Oklahoma between July 1981 and June 1984. All except 34 patients were white; 66% were male, and 34% were female.

Two control groups were selected. A hospital group of 313 patients were matched to the cases by age, sex, race, hospital, and date of admission. A second group of 336 sex- and age-matched population controls were selected by random-digit dialing. Information was obtained by direct interview. Relative risk for RCC was estimated from the odds ratio. The Biomedical Data Program (BMDP) statistical software packages were used to calculate summary ORs and 95% confidence limits according to the methods of Woolf [81]. The logistic

regression method and other multivariate techniques were also used to identify the relative importance of these factors.

The mean age of our study population was 60 years. The most important and significant findings of the case-population control analysis were as follows:

1. The lower the educational level attained, the higher the risk of RCC. A greater than twofold increase in risk was present for those with less than an 8th grade education (both men and women), and a significant increase in risk was present with lower educational levels in general.
2. Measurements of weight at age 20 and most recent and highest weights indicated that high relative weight as measured by body mass index (BMI = W/H^2(lbs/ft^2) appeared to be the principal risk factor in RCC. There was also a significant increase in risk with increase in relative weight for both men and women and a twofold increase in RCC risk (which was statistically significant) for a 30% increase in recent weight. Weight gain since age 20 did not in itself increase the risk for RCC. However, weight gain after age 20 was associated with a three- to fourfold increase in risk for those who were 20% or more overweight at age 20 and maintained their overweightness with time.
3. There was a weak positive association with cigarette smoking.
4. A positive association was found with use of artificial sweeteners, which was statistically significant in men only.
5. A weak positive association was found with coffee drinking, moderate to heavy tea drinking, and heavy use of decaffeinated coffee. The latter affected men only.
6. Significant increases of certain urologic, cardiovascular, and malignant diseases in men, digestive diseases in women, and metabolic diseases in both men and women were observed among the cases compared with controls. A history of hypertension or diabetes mellitus was more frequent in male cases than in controls and reached statistical significance for hypertension.
7. A negative association was found with beer, wine, liquor, and total alcohol consumption, and it was strongest for ever use of wine. The protection afforded by wine appeared to be limited to light use only (less than one glass per week).
8. Comparison of cases and controls for predominant lifetime occupation in men revealed a negative association with the professional occupation group and a positive association with the operatives occupation group that were statistically significant.
9. A statistically significant increase in risk was found for those who worked in petroleum refining and distributing (men) and dry cleaning (women) occupations.
10. Radiation therapy increased the risk of RCC; it was statistically significant for women only.
11. A positive association was found with use of medications for the treatment of cardiovascular diseases and hypertension in men only. Darvon use in women was associated with elevated risk. Use of Anacin or Bufferin was associated with increased risk of RCC in men.
12. Multivariate analyses for male cases ranked the most recent measurement of overweightness and exposure to petroleum refining and distributing products as the two most important etiological risk factors in RCC. Other significant risk factors included hypertension, kidney stones, sweetener use, lack of education, history of cancer, fast heart beat, smoking, genitourinary disease, and a history of diabetes mellitus. Wine consumption and a history of arthritis were significant negative risk factors.
13. Multivariate analyses for female cases ranked obesity at age 20 as the most important etiological factor in RCC. Other significant risk factors included digestive diseases, a history of benign tumors, lack of education, working as a dry cleaner, a history of metabolic disease, bladder infection, and the operators occupation group. Bladder infection and the operators profession were inversely related to RCC risk.

The most important findings of the case-hospital control comparisons are as follows:

1. High relative weight as measured by standard body mass index significantly increased the RCC risk in men. A recent weight gain of 30% increased the risk twofold in men only.
2. A weak positive association was found with cigarette use in men only. A significant 3.6-fold increase in risk was found among those who used snuff.
3. Coffee consumption in both men and women was strongly associated with RCC risk but reached statistical significance for women only.
4. No association was found with any type of alcohol consumption.
5. Of the occupational groups examined, being a professional provided a significant protection against RCC risk in both men and women, and the two groups of service workers (women) and farmers (men) were associated in a significant way with RCC risk.
6. There were several industries with elevated ORs: chemical manufacturing, machinery manufacturing, leather tanning, petroleum refining, dry cleaning, metal degreasing, and paper manufacturing. However, none of these high ORs reach statistical significance.
7. A number of diseases diagnosed 3 years prior to the interview increased the RCC risk. These included kidney stones (women), kidney injuries (men and women), prostatic cancer (men), and goiter (women).
8. The presence of polymastia increased RCC risk fourfold.
9. Sex hormone and other hormone use in men only provided protection against RCC.
10. Radiation therapy in women increased RCC risk by 50%.
11. Multivariate analyses for the male data showed that snuff use, genitourinary illness, obesity, and a history of arthritis were the three most important variables associated with increased RCC risk. Gastrointestinal illness, use of thyroid or other hormones, and the professional occupation group were inversely related to risk of RCC.
12. Multivariate analyses of the female data revealed a strong positive association for relative obesity, coffee consumption, kidney stones, clerical occupations, and use of sex hormones.

Results of the univariate and multivariate analyses show a clear association between obesity and renal cell carcinoma in both men and women, with the association being strong for men. The finding in women is consistent with four previously published reports. The finding in men is a new one and deserves special attention. The presence of an elevated risk in early adulthood (age 20) and the increased risk in old age suggests that obesity is capable of acting both as an initiator and as a promoter of renal carcinogenesis.

The weak positive association with cigarette smoking is less than what the results have been from prospective and retrospective studies. This could be explained by the high prevalence of cigarette smoking in the general population and the need for a larger sample size to detect a significant difference.

The increased risk associated with petroleum refining and distributing confirms the finding of other studies and reflects the carcinogen potential of hydrocarbon exposure. The positive association for dry cleaning in women confirms results from several proportionate mortality studies and is consistent with the petroleum finding in that the predominant solvent used in dry cleaning in Oklahoma is Stoddard compound, a petroleum derivative.

The negative association with wine consumption is new and intriguing. Both fats and hydrocarbons are soluble in alcohol. Alcohol, acting as a diuretic, may wash away many of the hydrocarbon compounds before they have time to work on the kidney in a harmful way.

The positive associations found with artifical sweeteners, hypertension, diabetes mellitus, cancer, and urologic, digestive, and metabolic diseases apparently reflect obesity.

Underlying etiologic factors could be high fat intake, hormonal imbalance, and arteriolonephrosclerosis, possibly making the kidney more susceptible to cancer.

RECOMMENDATIONS

The etiology of RCC remains obscure. The need exists for continuation of the case-control study approach to further delineate the role of suspected risk factors and to identify new ones. Special cohorts with identifiable and measurable exposure should be the focus of future research. Epidemiologic research into the etiology of RCC should focus on cigarette smoking, obesity, occupational factors, alcohol consumption, and genetic and familial factors.

The evidence to date on the role of cigarette smoking as an independent risk factor in RCC is not consistent. It is not clear what components of cigarette smoke are responsible, if any. Continuation of the case-control approach to study further the role of cigarette smoking is justified.

Obesity has emerged as the principal risk factor in both men and women, accounting for up to one-fourth of the RCC cases. Relative weight as measured by BMI and used in our study is but one measure of obesity. There are other more refined measures, both observational and biochemical, that should be incorporated into future case-control studies. It is not clear when and how obesity causes RCC. Studies should incorporate all correlates of obesity such as the habitual diet, hyperlipidemia, hypertension, and diabetes mellitus to clarify further the causes of obesity and the mechanisms of etiology.

Occupational factors appear to play a very important role in the etiology of RCC. Exposure to dry-cleaning solvents and to petroleum-related products are suspect. When possible, studies should focus on cohorts with identifiable and measurable exposure to estimate the risk of RCC directly. These cohorts have been identified in Oklahoma, and such studies are underway.

The inverse association with alcohol consumption and especially light consumption of wine is intriguing and must be explored further to determine the true nature of the association and to explain the mechanism. The interactions between alcohol consumption, obesity, and RCC deserve special attention.

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