Exhibit 224

A Case-Control Study of Renal Cell Carcinoma in Relation to Occupation, Smoking, and Alcohol Consumption

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ABSTRACT. A case-control study based on data from a cancer registry was conducted to evaluate the effects of smoking, alcohol use, and occupation on renal cell cancer risk. Information was obtained for 326 male and female cases and 978 age- and sex-matched controls. Elevated risks were identified for cigarette smokers and for men employed as truck drivers. No relationship between alcohol consumption and renal cancer was observed.

RELATIVELY FEW epidemiologic studies have examined the etiologic factors associated with renal cell cancer. Cigarette smoking is the most clearly established risk factor,[1] although several studies have failed to identify an association between smoking and renal cell cancer.[2–4] A recent study found an increased risk among men who chewed tobacco and a significant interaction between chewing tobacco and cigarette smoking.[4] Reports examining the role of alcohol consumption have been similarly inconclusive.[4–7] An elevated risk of renal cancer has been observed for occupations involving exposure to petroleum, tar, and pitch products,[7–9] and for insulation workers.[10] In an effort to evaluate further the relationship between these factors and renal cancer, a case-control study was conducted based on information collected by a cancer registry.

Methods

Subjects were identified through the Missouri Cancer Registry (MCR), which is maintained by the Missouri Department of Health. The registry has been collecting data on cancer cases from public and private hospitals since 1972, and reporting has been mandated by law since 1984. Cases were white Missouri residents diagnosed with histologically confirmed primary adenocarcinoma of the kidney between July 1984 and June 1986. Selection was limited to whites due to small numbers of other racial/ethnic groups. Cases had to be 20 yr or older at diagnosis. Controls were chosen from other patients in the registry diagnosed during the same time period. Tobacco-related sites (e.g., oral cavity, pancreas, larynx, lung, and bladder) were excluded from the control group to prevent an underestimation of the smoking-associated risk of renal cancer. For each case, three white controls were frequency-matched by age group. A total of 326 cases (205 males and 121 females) and 978 controls (615 males and 363 females) were identified. The control group consisted of cancers of the small intestine, colon, rectum, hematopoietic and reticuloendothelial systems, skin, prostate, nervous system, and lymph nodes.

The MCR systematically collects data on smoking history, alcohol consumption, and occupational history. Reporting of these variables is mandatory for Missouri hospitals. Hospital registrars record information for cancer patients using a standardized protocol, and these data are subsequently coded and checked by trained medical records technicians on the MCR staff. Information on smoking history and alcohol use is collected at the time of cancer diagnosis. These data are characterized according to status (i.e., never, former,

or current use) and by the average daily amount smoked or drunk. Longest held job is recorded as usual occupation and coded by the MCR according to the 1980 United States census codes[11] to insure uniformity in coding.

The measure of association between various risk factors and renal cell cancer was the odds ratio (OR). Stratified analyses were conducted by the Mantel-Haenszel method,[12] and the Mantel extension test[13,14] was used to evaluate the linearity of trends. Unconditional logistic regression models were used to obtain maximum likelihood estimates of the OR and 95% confidence intervals.[15,16] All results presented were based on logistic regression because it allowed for simultaneous adjustment for multiple factors. For work history analyses, occupations with three or more cases were compared with all other occupations and with a low-risk employment category. The low-risk category was that in which workers were likely to have few occupational exposure to carcinogens. Low-risk occupations included professionals, managers, sales, and clerical workers (census codes 1–389). Subjects with unknown or missing information were excluded from the relevant analyses.

Results

Table 1 presents the risk estimates for renal cell cancer associated with smoking and alcohol consumption. The largest risk for ever smoking was observed among females (OR = 1.87). Risk associated with ever smoking was also elevated for both sexes combined. Increasing trends in ORs were identified for level of current smoking among males (p = .02) and among both sexes combined (p = .01). Among females, a slight inverse association between renal cancer risk and level of current smoking was observed (p = .29). The "other tobacco" category included snuff, cigars, and pipes and showed no excess risk. No unusual risk was observed for alcohol history for either sex. Similarly, there were no trends in risk according to average number of drinks consumed per day (not shown).

Risk estimates are shown for the occupational categories that had three or more cases and an elevated crude OR (Table 2). The largest OR was observed for heavy truck drivers, with an approximate three-fold risk. Occupations with slightly elevated ORs included automobile mechanics, machinists, and construction supervisors and laborers.

Discussion

The present study found an excess renal cancer risk of 1.4 associated with cigarette smoking, which is similar to some previous estimates.[7,17,18] Although occupational results were based on small numbers, and the possibility of chance findings exists, the significantly elevated risk among truck drivers and the weaker association observed for mechanics may be related to aromatic hydrocarbon exposure from gasoline vapor or exhaust fumes. A recent laboratory study[19] found that exposure to unleaded gasoline vapor caused kidney carcinomas in male rats. Epidemiologic studies have not generally supported this association,[20,21] although a recent report suggested a slight upward trend in renal cancer risk associated with duration of gasoline station employment.[21] An increased risk of bladder cancer has been observed for truck drivers and auto mechanics,[22–24] but no similar association has been reported for kidney cancer. This study also found a nonsignificantly elevated risk among machinists, which has been observed for bladder cancer.[22,25] Because cigarette smoking has been estimated to account for 30% of renal cell cancer among males and 24% among females,[7] it is important to continue to develop alternative etiologic hypotheses.

Selection and information bias must be considered when interpreting these findings. The advantages and disadvantages of the use of cancer controls have been discussed in detail.[26] The likelihood that cancer patients may change their jobs or smoking habits after di-

Table 1.—Adjusted Odds Ratios* (OR) and 95% Confidence Intervals (CI) for Renal Cell Carcinoma According to Smoking History and Alcohol Consumption

Factor	Males			Females			Both sexes		
	N	OR (95% CI)		*N*	OR (95% CI)		*N*	OR (95% CI)	
Smoking history									
Never smoked	292	1.0		286	1.0		578	1.0	
Ever smoked	367	1.3	(0.9–1.9)	115	1.8	(1.0–3.0)	482	1.4	(1.0–1.9)
Other tobacco	42	0.8	(0.4–1.9)	1			43	0.8	(0.3–1.7)
Unknown	119	0.8	(0.4–1.7)	82	1.2	(0.4–3.1)	201	0.9	(0.5–1.7)
Cigarettes/day (current smokers)									
<20	79	1.0	(0.5–1.7)	32	1.6	(0.7–3.8)	111	1.1	(0.7–1.8)
20+	127	1.8	(1.1–2.9)	46	1.2	(0.5–2.6)	173	1.6	(1.1–2.5)
Alcohol consumption									
Never drank	380	1.0		291	1.0		671	1.0	
Ever drank	274	0.9	(0.6–1.3)	91	1.1	(0.6–2.0)	365	1.0	(0.7–1.4)
Unknown	166	1.1	(0.6–2.1)	102	0.8	(0.3–2.0)	268	1.0	(0.6–1.7)

*Adjusted for age, smoking, alcohol use and sex, when appropriate.

Table 2.—Adjusted Odds Ratios* (OR) and 95% Confidence Intervals (CI) for Renal Cell Carcinoma According to Usual Occupation, Males

Occupational category	Cases (*N*)	Controls (*N*)	OR_1† (95% CI)	OR_2† (95% CI)
Automobile mechanics	3	5	1.8 (0.4–2.0)	1.9 (0.4–8.3)
Construction supervisors	3	6	1.5 (0.4–6.0)	1.5 (0.4–6.4)
Machinists	3	4	2.2 (0.5–10.3)	2.2 (0.5–10.3)
Truck drivers, heavy	8	8	3.1 (1.1–8.5)	3.0 (1.1–8.6)
Construction laborers	3	6	1.3 (0.3–5.5)	1.5 (0.3–6.2)

*Adjusted for age, smoking, and alcohol use by logistic regression.
†OR_1 based on comparison with all other occupations; OR_2 based on comparison with low-risk occupations (census codes 1–389).

agnosis may systematically bias a study using general population controls. The current study is unlikely to have this type of bias. Perhaps the greatest liability of using cancer controls is that the OR that is estimated does not refer to the risk of disease relative to remaining healthy.[26] In this study, a number of different cancer types were included in the control group in an attempt to minimize bias associated with the use of cancer controls.

Many occupational studies have compared each employment category with all other occupations. Such analyses may underestimate risk and may fail to identify some high-risk occupations.[24] To address this potential bias, occupational analyses were initially conducted by comparing each category with all other occupations. A second set of analyses compared each category with occupations deemed to be low risk. The results suggested little difference in the two comparisons. The occupational information available in this study was relatively crude and reflected only usual employment. It is probable that some degree of misclassification was present; however, it is unlikely that cases and controls were differentially misclassified. Thus, any bias due to misclassification would tend toward the null value.[27]

Two other limitations of the present study deserve mention. First, no information was available on body mass, which has been implicated as a risk factor in at least three studies.[4,6,7] And second, the lack of data on socioeconomic status made it impossible to adjust for the effects of education and income. The current findings are preliminary and require confirmation in large studies with more detailed occupational information.

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