ABSTRACT

The relationship between smoking habits and the risk of renal cell carcinoma was investigated in a case-control study conducted in northern Italy on 131 cases of histologically confirmed cancers of the renal parenchyma (85 males, 46 females) and 394 controls in hospital for acute, nonneoplastic, nonurological disorders. Compared with never smokers, the relative risk (RR) was 1.7 (95% confidence interval = 1.0–3.1) among ex-smokers. A direct and significant dose-risk relationship was observed among current smokers, with RR of 1.1, 1.9, and 2.3 for moderate, intermediate, and heavy smokers. This trend in risk was statistically significant ($\chi^2 = 5.04; P = 0.02$). The risk was directly related with duration of smoking (RR = 1.7 for <30 versus 1.8 for ≥30 years, $P = 0.04$), and inversely with age at starting (RR = 2.0 for ≤20 versus 1.7 for >20 years) and, among ex-smokers, with time elapsed since stopping (RR = 2.2 for <10 versus 1.3 for ≥10 years). This pattern of risk, together with the absence of appreciable confounding, adds further evidence for a causal nature of the association between smoking and renal cell cancer.

INTRODUCTION

Although the kidney is commonly considered one of the tobacco-related cancer sites, the evidence for the association is, at least in quantitative terms, still not fully understood. The estimated mortality ratios in five cohort studies ranged between 1.2 and 2.7 (1–5), whereas the relative risk in seven case-control studies which specifically considered renal cell carcinomas ranged between 1.1 and 5.1 (6–12).

Part of the heterogeneity of these results may be due to the misclassification, in some series, of renal cell carcinomas with cancers arising from the renal pelvis, which are strongly tobacco related (13, 14). Nonetheless, this could hardly explain such broad variability, and further quantitative information on the issue is therefore needed.

Thus, this article considers the relationship between smoking and adenocarcinoma of the kidney in a case-control study conducted in northern Italy.

SUBJECTS AND METHODS

The data were derived from a case-control study of several urinary tract neoplasms under way since January 1985 in the Greater Milan area, northern Italy.

Within the general design of the investigation, previously described in relation to the bladder cancer study (15), trained interviewers identified and questioned patients admitted to a network of teaching and general hospitals in the area under surveillance for kidney cancer (cases) and a wide spectrum of acute, nonneoplastic, nonurological or genito-urinary tract conditions (controls). Participation was almost complete, since less than 3% of cases and controls approached for interview refused to participate. The present analysis is based on data collected before October 1989.

The structured questionnaire included information on sociodemographic factors and personal characteristics and habits; use of alcohol in various forms and use of coffee and other methylxanthine-containing beverages; a few selected indicator foods; a problem-oriented medical history; a specific drug use history; and history of occupation or occupational exposure.

The subjects were asked whether they were current smokers, had smoked in the past, or were lifelong nonsmokers. Those who had smoked at least one cigarette (or pipe/cigar) per day for at least 1 year. Those who had smoked within the year before the interview were classified as current smokers, and those who had stopped smoking at least 1 year before interview as ex-smokers. The smokers and ex-smokers were asked to specify the total duration of the habit (in years) and the average quantity smoked per day.

Cases. The cases were 131 subjects under the age of 75 (85 males, 46 females) with histologically confirmed adenocarcinoma of the kidney—after specific exclusion of cancers of the renal pelvis—diagnosed within the year before the interview, who had been admitted to the National Cancer Institute, to several university clinics (chiefly of surgery), or to the Ospedale Maggiore, which includes the four largest teaching and general hospitals in Milan. The median age was 60 years.

Controls. The controls were 394 subjects (296 males, 98 females), admitted for acute conditions to the same network of hospitals where cases had been identified. Of these, 30% were admitted for traumas, 17% for nontraumatic orthopedic conditions, 13% for acute medical, 6% for surgical diseases, and 34% for other miscellaneous disorders, such as skin, ear, nose and throat, or dental ailments. The median age was 60 years, and the distribution of cases and controls according to sex, age group, and other relevant covariates (social class and education) is given in Table 1. The catchment areas of cases and controls were well comparable: overall, 79% of the cases and 83% of the controls resided in the same region, Lombardy, and 88% of the cases and 90% of the controls came from northern Italy. Cases and controls had to be in hospital at the time of interview. All of the interviews were conducted in hospital, and proxy interviews were not conducted for deceased patients.

Data Analysis and Control of Confounding. Relative risks of kidney cancer, together with their 95% approximate confidence intervals (16), according to various smoking-related variables were first derived from data stratified by sex and quinquennia of age by the Mantel-Haenszel procedure (17). Significance was assessed by means of the linear test described by Mantel (18). To account simultaneously for the potential confounding effect of various a priori identified factors, multiple logistic regression was used (16, 19), including terms for age, sex, area of residence, education, and body mass index.

RESULTS

Cases of renal cell carcinoma were similar to controls as regards education and social class, although a slightly smaller proportion of cases was in the lowest categories of both socioeconomic indicators (Table 1).

Smoking status and number of cigarettes per day are considered in Table 2. Compared with never smokers, the RR was 1.9 (95% CI = 1.0–3.6) among ex-smokers. A direct and significant dose-risk relationship was observed among current smokers, with RRs of 1.3, 2.0, and 2.1 for moderate, intermediate, and heavy smokers. The trend in risk was statistically significant ($\chi^2 = 5.31; P = 0.02$). The association was observed in males

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3 The abbreviations used are: RR, relative risk; CI, confidence interval.
and females but was less clear in females (RR for female smokers = 1.3, 95 CI = 0.4–3.0) and was somewhat stronger for smokers of high tar (≥22 mg) cigarettes (RR = 2.2, 95 CI 1.0–4.6). Probably on account of limited absolute numbers, however, there was no significant heterogeneity in relation to those variables.

Other measures of exposure of tobacco smoking are considered in Tables 3 and 4. The risk was directly related to duration (RR = 2.0 for <30 versus 2.2 for ≥30 years, \( \chi^2 \), 6.11; \( P = 0.02 \); Table 3), and inversely related with age at starting (RR = 2.5 for <20 versus 1.8 for ≥20) and, among ex-smokers, with time elapsed since stopping (RR = 2.6 for <10 versus 1.3 for ≥10 years; Table 4).

Allowance for a number of identified potential distorting factors, including sociodemographic indicators and body mass index (a factor potentially related both to smoking and renal cell cancer), did not appreciably modify any of the tobacco-related risks. In this study, the association between body mass index and renal cell carcinoma was not significant (RR for obese versus leaner subjects = 1.4, 95 CI = 0.8–2.5), but smokers tended to be leaner than controls.

### DISCUSSION

The present study provides additional quantitative evidence on the smoking-renal cancer association. The risk was significantly above unity both in ex- and current smokers, and there were significant trends in risk with dose and duration; furthermore, the risk was higher in smokers who had started at younger age, and it declined after cessation of exposure. This pattern of risk, together with the absence of any substantial apparent confounding, strongly supports the causal nature of the association.

These results are in broad agreement with the overall evidence from previous case-control studies (6–12), summarized in Table 5. The relative risk was above unity in all seven published studies, and, although the different estimates appear to vary widely (between 1.1 and 5.1), most studies show a relative risk for smokers around a factor of 2. Such an estimate is consistent with the risk observed in cohort studies as well, in which relative risk ranged from 1.2 in a Japanese cohort (4) to 2.7 in the British physicians study (5).

An approximately 2-fold increased risk of renal cell cancer in smokers appears, therefore, as a reasonable estimate of the kidney cancer/smoking association from published studies. In quantitative terms, this confirms the importance of tobacco in renal cell carcinogenesis, although the RR is probably lower than for transitional cell cancer of the bladder and other urinary tract tumors. Preliminary results from a companion study of bladder cancer conducted in the same population, in fact, gave an overall RR for smokers of 2.9 (15), and the risk estimates were even higher (i.e., between 2.7 in moderate and 9 in heavy smokers) in another cancer-control study from northern Italy (20). This association finds plausible biological interpretations, since most substances or metabolites are excreted through the urinary tract and are consequently in contact with kidney cells, and the urine of smokers shows increased mutagenic activity.

### Table 1 Distribution of 131 cases of kidney cancer and 394 controls according to sex, age, education, and social class, Milan, Italy, 1985–1989

<table>
<thead>
<tr>
<th></th>
<th>Kidney cancer</th>
<th>Controls</th>
<th>Relative risk estimates (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td>No. %</td>
<td>M-H*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td>No. %</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age group (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td>26</td>
<td>19.8</td>
<td>59</td>
</tr>
<tr>
<td>50–59</td>
<td>38</td>
<td>29.0</td>
<td>121</td>
</tr>
<tr>
<td>60–69</td>
<td>52</td>
<td>39.7</td>
<td>170</td>
</tr>
<tr>
<td>70–74</td>
<td>15</td>
<td>11.5</td>
<td>44</td>
</tr>
<tr>
<td>Education (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;7</td>
<td>69</td>
<td>52.7</td>
<td>225</td>
</tr>
<tr>
<td>7–11</td>
<td>37</td>
<td>28.2</td>
<td>95</td>
</tr>
<tr>
<td>≥12</td>
<td>25</td>
<td>19.1</td>
<td>72</td>
</tr>
<tr>
<td>Unknown</td>
<td>2</td>
<td>12.2</td>
<td>54</td>
</tr>
</tbody>
</table>

* Based on the head of the household’s occupation.

### Table 2 Distribution of 131 cases of kidney cancer and 394 controls according to smoking habits, Milan, Italy, 1985–1989

<table>
<thead>
<tr>
<th></th>
<th>Kidney cancer</th>
<th>Controls</th>
<th>Relative risk estimates (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking habit (cigarettes/day)</td>
<td></td>
<td></td>
<td>M-H*</td>
</tr>
<tr>
<td>Never smokers</td>
<td>50</td>
<td>168</td>
<td>1.0</td>
</tr>
<tr>
<td>Ex-smokers</td>
<td>32</td>
<td>96</td>
<td>1.9 (1.0–3.6)</td>
</tr>
<tr>
<td>Smokers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;15</td>
<td>11</td>
<td>42</td>
<td>1.3 (0.6–2.6)</td>
</tr>
<tr>
<td>15–24</td>
<td>25</td>
<td>60</td>
<td>2.0 (1.1–3.8)</td>
</tr>
<tr>
<td>≥25</td>
<td>13</td>
<td>28</td>
<td>2.1 (1.0–4.6)</td>
</tr>
</tbody>
</table>

* Mantel-Haenszel estimates adjusted for age and sex.

### Table 3 Distribution of 131 cases of kidney cancer and 394 controls according to duration of smoking, Milan, Italy, 1985–1989

<table>
<thead>
<tr>
<th>Duration of smoking (years)</th>
<th>Kidney cancer</th>
<th>Controls</th>
<th>Relative risk estimates (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never smokers</td>
<td>50</td>
<td>168</td>
<td>1.0</td>
</tr>
<tr>
<td>&lt;30</td>
<td>33</td>
<td>86</td>
<td>2.0 (1.1–3.6)</td>
</tr>
<tr>
<td>≥30</td>
<td>47</td>
<td>128</td>
<td>2.2 (1.2–3.9)</td>
</tr>
</tbody>
</table>

* Mantel-Haenszel estimates adjusted for age and sex.
Although at least one substance (dimethylnitrosamine) present in tobacco smoke causes kidney cancer in rats (22), the role of various groups of carcinogens found in tobacco smoke on kidney carcinogenesis is not established (14).

Since this is a typical hospital-based case-control study, estimates of smoking relative risks can be criticized a priori in terms of potential unrepresentativeness of the hospital controls for the smoking habits. A bias might be introduced, for instance, by prolonged hospital stay among smokers, with a consequently greater probability of being interviewed. However, data from the 1983 Italian National Health Survey do not support this hypothesis, since the duration of hospital stay was comparable for smokers and nonsmokers (23). Within the dataset of this study, moreover, smoking habits were comparable across various diagnostic categories of the controls. In relation to other possible sources of bias, although the study was not population based and only cases and controls present in the hospitals during the interviewers' visit were included, participation of controls of smoking relative risks can be criticized a priori in terms of potential unrepresentativeness of the hospital controls for the smoking habits. A bias might be introduced, for instance, by prolonged hospital stay among smokers, with a consequently greater probability of being interviewed. However, data from the 1983 Italian National Health Survey do not support this hypothesis, since the duration of hospital stay was comparable for smokers and nonsmokers (23). Within the dataset of this study, moreover, smoking habits were comparable across various diagnostic categories of the controls. In relation to other possible sources of bias, although the study was not population based and only cases and controls present in the hospitals during the interviewers' visit were included, participation of subjects identified was practically complete, cases and controls came from similar catchment areas, and allowance for a number of identified potential distorting factors did not materially modify any of the estimates.

In conclusion, therefore, this study confirms that cigarette smoking is an important—and probably the single best defined—cause of renal cell cancer, although the strength of the association is apparently smaller than for bladder and other urinary tract neoplasms.

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