


Notes

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Concordance of Genetic Alterations in Poorly Differentiated Colorectal Neuroendocrine Carcinomas and Associated Adenocarcinomas

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Background: The histopathologic spectrum of colorectal neuroendocrine tumors ranges from benign to highly malignant. In this spectrum, poorly differentiated neuroendocrine carcinoma (PDNC) is the most aggressive type, characterized by early dissemination and a rapidly fatal course. Since it is unclear whether PDNC originates from neoplastic transformation of pre-existing neuroectodermal cells, pluripotent epithelial stem cells, or adenocarcinoma precursor cells, we investigated the histogenesis of this type of cancer by performing genetic analyses on a series of colorectal tumors.

Methods: Archived histologic sections of colorectal PDNC from nine patients were analyzed; gastrointestinal carcinoid tumor specimens from four patients were used as controls. The specimens were deparaffinized, microdissected, and analyzed genetically. After DNA extraction, polymerase chain reaction amplification was performed to investigate alteration (i.e., loss of heterozygosity [LOH]) of the APC (adenomatous polyposis coli), DCC (deleted in colorectal carcinoma), and p53 (also known as TP53) genes. Results: LOH of the APC, DCC, or p53 genes was observed in six of eight informative PDNC tumors; no LOH was detected in the carcinoid control specimens. Four of five informative PDNC tumors had associated adenocarcinoma; LOH of the APC and p53 genes in these tumors involved the same allele in both tissue components. Four of the five tumors with associated adenocarcinoma showed LOH of the DCC gene; in three of these four tumors, the PDNC and adenomatous components showed LOH of the same allele. Conclusions: PDNC and associated adenocarcinoma appear to be derived from the same cell of origin, which is most likely either a pluripotent epithelial stem cell or an adenocarcinoma precursor cell. [J Natl Cancer Inst 1997;89:1448–53]

Colorectal neuroendocrine tumors comprise a wide histopathologic spectrum that ranges from benign to highly malignant (1). Within this spectrum, poorly differentiated neuroendocrine carcinoma (PDNC) clearly represents the most aggressive neoplasm and is characterized by early dissemination and a rapidly fatal course (2).

In 1949, ‘‘anaplastic polygonal-celled carcinoma’’ or ‘‘carcinoma simplex’’ was recognized by Dukes (3) as a neoplasm with a particularly poor prognosis compared with that for all other types of rectal adenocarcinomas. The characteristic histopathologic features of PDNC have subsequently been interpreted as ‘‘neuroendocrine differentiation’’ based on ultrastructural and immunohistochemical studies. Neurosecretory-type dense core granules may be demonstrated upon ultrastructural examination (4–6), and the tumors may show positive immunoreactivity with anti-neuron-specific enolase (NSE) (2,6,7) and anti-chromogranin A (7).

Although the cells of colorectal PDNC tend to be small and have hyperchromatic nuclei containing coarse, clumped chromatin (hence, commonly termed ‘‘small-cell carcinoma’’), the presence of scattered bizarre mononucleated and multinucleated tumor cells with large hyperchromatic nuclei (4,5) or large vesicular nuclei (2) is not unusual. The term ‘‘small-cell carcinoma’’ reflects pheno-
typical similarities with high-grade neuroendocrine carcinomas of the lung rather than an understanding of the histogenesis of neuroendocrine colorectal carcinoma. In fact, it is currently unknown whether PDNC is derived from pre-existing neuroectodermal cells or from pluripotent stem/adenocarcinoma cells.

Alterations of the APC (adenomatous polyposis coli) gene, the DCC (deleted in colorectal carcinoma) gene, and the p53 (also known as TP53) gene, the so-called “adenoma–adenocarcinoma sequence,” have been strongly associated with colorectal carcinogenesis (8). Allelic deletion of the APC gene represents an early event in gastrointestinal cancerogenesis (9) and has been shown to even precede histopathologic changes in Barrett’s esophagus syndrome (10).

To better elucidate the histogenesis of neuroendocrine colorectal carcinomas, we performed a genetic analysis of a series of neuroendocrine carcinomas that occurred solitary or in association with adenocarcinomas and/or adenomas. By utilizing a microdissection technique, we obtained selected areas of neuroendocrine carcinoma, adenocarcinoma, and adenoma and normal control tissue and analyzed them for loss of heterozygosity (LOH) of the genes of the adenoma–adenocarcinoma sequence.

Subjects and Methods

Patients/Tumors

Nine specimens from nine patients diagnosed with primary colorectal PDNC were retrieved from the files of the Laboratory of Pathology, National Cancer Institute (four specimens), and the Department of Pathology and Laboratory Medicine, Hospital of the University of Pennsylvania (five specimens) (Table 1). In all patients (male-to-female ratio = 5:4; average age, 49 years; age range, 36–60 years), the tumor had been surgically resected. The tumors had occurred as pure PDNC (specimens 8 and 9) or in association with adenocarcinoma or adenoma (specimens 1–7) (Fig. 1). Four PDNCs were associated with adenocarcinoma (specimens 1–4), one PDNC was associated with adenoma (specimen 5), and two tumors occurred in association with both tubulo-villous adenoma and adenocarcinoma (specimens 6 and 7). The architecture of the neuroendocrine tumors showed sheets, nests, or trabeculae of tumor cells. In general, the neuroendocrine tumor cells were rather uniform in appearance, with hyperchromatic nuclei showing coarse, clumped chromatin. In some tumors, however, there were foci of moderate-to-marked pleomorphism. When present, the adenocarcinoma component consisted of invasive tumor with characteristic glandular architecture.

In all biphenotypic cases, the PDNC component and the adenocarcinoma component occurred as separate masses with distinct morphology. When areas of adenocarcinoma and PDNC collided, intermingling of tumors with different morphology could be observed (Fig. 1).

Table 1. Analysis of colorectal tumors: clinical data*

<table>
<thead>
<tr>
<th>Specimen No.</th>
<th>Age, y/sex of patient</th>
<th>Tumor location</th>
<th>Tumor histology</th>
<th>Immunohistochemical profile of PDNC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>58, male</td>
<td>Cecum</td>
<td>PDNC</td>
<td>+:chrom, chro</td>
</tr>
<tr>
<td>2</td>
<td>40, male</td>
<td>Ascending colon</td>
<td>PDNC</td>
<td>+: syn, chro</td>
</tr>
<tr>
<td>3</td>
<td>50, male</td>
<td>Rectum</td>
<td>PDNC</td>
<td>+: syn, vin</td>
</tr>
<tr>
<td>4</td>
<td>54, female</td>
<td>Transverse and descending colon</td>
<td>PDNC</td>
<td>+: ker, syn, chro</td>
</tr>
<tr>
<td>5</td>
<td>60, female</td>
<td>Ascending colon</td>
<td>PDNC</td>
<td>+: ker, syn, chro</td>
</tr>
<tr>
<td>6</td>
<td>36, female</td>
<td>Ascending colon</td>
<td>PDNC</td>
<td>+: ker, chro</td>
</tr>
<tr>
<td>7</td>
<td>50, female</td>
<td>Cecum</td>
<td>PDNC</td>
<td>+: ker, CEA, vin, chro</td>
</tr>
<tr>
<td>8</td>
<td>37, male</td>
<td>Ascending colon</td>
<td>PDNC</td>
<td>ND</td>
</tr>
<tr>
<td>9</td>
<td>56, male</td>
<td>Rectum</td>
<td>PDNC</td>
<td>+: ker, chro, Leu7 antigen</td>
</tr>
<tr>
<td>10</td>
<td>74, male</td>
<td>Ileum</td>
<td>Carcinoid†</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>68, male</td>
<td>Rectum</td>
<td>Carcinoid†</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>76, male</td>
<td>Jejunum</td>
<td>Carcinoid†</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>44, female</td>
<td>Small bowel</td>
<td>Carcinoid†</td>
<td></td>
</tr>
</tbody>
</table>

*PDNC = poorly differentiated neuroendocrine carcinoma; PD = poorly differentiated; MD = moderately differentiated; + = positive by immunohistochemistry; − = negative by immunohistochemistry; chro = chromogranin; LCA = leukocyte common antigen; syn = synaptophysin; vim = vimentin; ker = keratin; NSE = neuron-specific enolase; CEA = carcinoembryonic antigen; ND = not done.

†Control group consisted of four gastrointestinal carcinoids originating in the small bowel (midgut) or rectum (hindgut).

Microdissection

Unstained 5-μm sections on glass slides were deparaffinized with xylene, rinsed in 100%, 90%, and 80% ethanol, briefly stained with hematoxylin-eosin, and rinsed in 10% glycerol in Tris-EDTA buffer. A slightly modified microdissection procedure was performed under direct light microscopic visualization with the use of a 30-gauge needle as previously described (11). Tumor cells were obtained from PDNC areas (specimens 1–9). Whenever available, the following areas were also dissected: tubulo-villous adenoma (specimens 5–7) and/or adenocarcinoma (specimens 1–4, 6, and 7). In one patient, metastatic tumor cells were selectively obtained from regional lymph nodes involved by either adenocarcinoma or neuroendocrine carcinoma (specimen 6). From the intestinal carcinoid tumors, neuroendocrine tumor cells were selectively obtained. Control tissue for analysis of constitutional DNA included normal mucosal tissue and/or submucosal lymphoid tissue.
DNA Extraction

Procured cells were immediately resuspended in 10–20 μL buffer containing Tris–HCl (pH 8.0), 10 mM EDTA (pH 8.0), 1% Tween 20, and 0.1 mg/mL proteinase K and incubated at 37 °C overnight. The mixture was then boiled for 10 minutes to inactivate the proteinase K, and 1.5 μL of this solution was used for polymerase chain reaction (PCR) amplification of the DNA.

Primers and PCR Conditions

All specimens were examined for LOH with different microsatellite markers for loci of the APC gene at 5q (DSS346 and APC II; Research Genetics, Huntsville, AL), the DCC gene at 18q (DCC; Research Genetics), and p53 at 17p (TP53; Research Genetics). In one specimen (No. 6), APC LOH was also analyzed with the marker D5S299 (Research Genetics). Each PCR sample contained the following: 1.5 μL of template DNA as described above; 10 pmol of each primer; 20 nmol each of deoxyadenosine triphosphate, deoxycytidine triphosphate, dCTP), deoxyguanosine triphosphate, and deoxythymidine triphosphate; 15 mM MgCl₂; 0.1 U Taq DNA polymerase; 0.05 μL [32P]dCTP (6000 Ci/mmol); and 1 μL of 10× PCR buffer (The Perkin-Elmer Corp., Foster City, CA) in a total volume of 10 μL. PCR was performed under the following conditions: 35 cycles, denaturing of DNA at 95 °C for 1 minute, annealing of primer and template DNA at 55 °C for 1 minute with DSS346, APC II and p53 (at 56 °C for 1 minute with DCC), and extending of primer DNA at 72 °C for 90 seconds. The final extension was continued for 10 minutes.

LOH Analysis

Labeled amplified DNA was mixed with an equal volume of formamide loading dye (95% formamide, 20 mM EDTA, 0.05% bromophenol blue, and 0.05% xylene cyanol). Samples were then denatured for 5 minutes at 95°C, loaded onto a gel consisting of 6% acrylamide (acrylamide–bisacrylamide, 49:1), and subjected to electrophoresis at 1800 V for 90 minutes. After electrophoresis, the gels were transferred to 3-mm Whatman paper and dried. Autoradiography was performed with Kodak X-OMAT film (Eastman Kodak, Rochester, NY).

A tumor specimen was considered informative for a polymorphic marker if normal tissue DNA showed two different alleles (heterozygosity). The criterion for LOH was complete or nearly complete absence of one allele in the tumor DNA as defined by direct visualization.

Results

APC Gene Deletions

In all nine specimens, PDNC cells and, if present, cells from associated neoplasms were selectively microdissected (Fig. 1). In addition, normal lymphoid tissue and/or normal mucosal tissue was obtained to analyze constitutive DNA for control.

LOH analysis was performed with DSS346 for the APC gene. In one case, LOH analysis was also performed with DSS299 (specimen 3). Three specimens (Nos. 1, 6, and 8) showed LOH, three specimens (Nos. 3, 5, and 7) showed no LOH, and three specimens (Nos. 2, 4, and 9) were noninformative (Table 2, Fig. 2). In all three specimens with APC gene deletion, APC LOH was observed in the PDNC component, and identical allelic loss was seen in the associated adenocarcinomatous lesions (specimens 1 and 6).

In all specimens that were noninformative or that showed no LOH with DSS346, the results were identical in all tumor components, including neuroendocrine carcinoma and adenocarcinoma and/or adenoma. Three specimens that either were noninformative (specimen 4) or showed no LOH (specimens 5 and 7) with DSS346 were also analyzed with APC II, another microsatellite marker for the APC gene area. That analysis revealed homozygosity in specimen 4 and no LOH in all tumor components in specimens 5 and 7.

Four carcinoid tumors (specimens 10–13) were tested for LOH with DSS346. All four showed no LOH with this
Fig. 2. Representative results of loss of heterozygosity (LOH) analysis. Arrowheads indicate allelic losses. A) Analysis of different components of specimen 6 with DSS299 for changes of the APC (adenomatous polyposis coli) gene (5q). 1 = lymphoid tissue; 2 = dysplasia; 3 = dysplasia; 4 = invasive adenocarcinoma; 5 = neuroendocrine carcinoma; 6 = dysplasia; 7 = lymph node metastasis of neuroendocrine carcinoma; 8 = lymph node metastasis of adenocarcinoma. The selected areas of adenoma, adenocarcinoma, neuroendocrine carcinoma, and tumor metastatic to regional lymph nodes show loss of the lower allele (lanes 2–8); no LOH is seen in control lymphoid tissue (lane 1). B) Analysis of carcinoid tumor (specimen 13) for changes of the APC gene (5q) with DSS346, showing no LOH. T = tumor tissue; N = normal lymphoid tissue. C) Analysis of carcinoid tissue (specimen 13) with APC II (5q), showing no LOH. T = tumor tissue; N = normal lymphoid tissue. D) Analysis of neuroendocrine carcinoma (specimen 8) with DCC (deleted in colorectal carcinoma) marker for changes of the DCC gene (18q). Loss of the lower allele is seen in tumor tissue. 1 = rectal mucosa; 2 = neuroendocrine carcinoma; 3 = lymphoid tissue; 4 = neuroendocrine carcinoma. E) Samples of different tumor components (specimen 6), showing allelic deletion of different alleles. 1 = normal mucosa; 2 = dysplasia; 3 = adenocarcinoma; 4 = neuroendocrine carcinoma; 5 = lymphoid tissue. F) LOH of neuroendocrine carcinoma (specimens 8 and 9) with TP53 (17p) (lanes 1–5: specimen 8; lanes 6–10: specimen 9). Specimen 8 shows loss of upper allele in tumor tissue. 1 = normal mucosa; 2 = lymphoid tissue; 3 = neuroendocrine carcinoma; 4 = lymphoid tissue, different area; 5 = neuroendocrine carcinoma specimen 9 shows loss of upper allele in tumor tissue; 6 = normal mucosa; 7 = normal mucosa; 8 = normal lymphoid tissue; 9 = neuroendocrine carcinoma; 10 = neuroendocrine carcinoma, different area.

Allelic losses of or within chromosome 5q have been observed in 20%–50% of colorectal carcinomas and in about 30% of colorectal adenomas (18). In the present study, three of the six informative neuroendocrine carcinomas showed APC gene deletion (specimens 1, 6, and 8). In addition, whenever APC LOH was present in different tumor components, loss of the same allele (identical allelic loss) was observed. In the biphenotypic specimens 1 and 6, both neuroendocrine carcinoma and adenocarcinoma and/or adenoma showed identical allelic loss (Table 2, Fig. 2). Conversely, in the biphenotypic cases with retained heterozygosity of the APC gene, there was no LOH in any neoplastic component analyzed (specimens 3, 5, and 7).

Therefore, whenever allelic deletion was present in the adenocarcinoma component, it was also present in the PDNC component. Whenever heterozygosity was retained in the adenocarcinoma component, it was also retained in the neuroendocrine carcinoma component. Both the presence of APC gene deletion in PDNC and the identity of the allelic loss in the associated neoplastic lesions support the hypothesis that the neuroendocrine carcinoma component is derived from an epithelial stem or adenocarcinoma precursor cell.

We observed DCC LOH in four biphenotypic specimens. In three of these specimens, there was identical allelic loss in the neuroendocrine carcinoma and the associated adenoma and/or adenocarcinoma lesions. In one specimen (No. 6), there was allelic loss of opposite alleles in the adenoma component compared with the adenocarcinoma component, as well as in the adenocarcinoma component compared with the PDNC component. Since the same specimen had shown identical allelic loss of the APC gene in all areas examined (Fig. 2), we speculate that the DCC gene changes in this specimen result from independent events during tumor progression from adenoma to adenocarcinoma. In addition, we observed identical allelic loss of the p53 gene in two biphenotypic specimens.

PDNC is a highly aggressive neoplasm that may be observed in association with villous adenoma (2,5), adenocarcinoma (6), or adenocarcinomatous elements (12–14). In this study, we performed genetic analysis of nine colorectal PDNCs. Seven of these cases were associated with adenocarcinoma and/or adenoma (specimens 1–7); two cases had occurred as pure PDNC (specimens 8 and 9).

Discussion

PDNC is a highly aggressive neoplasm that may be observed in association with villous adenoma (2,5), adenocarcinoma (6), or adenocarcinomatous elements (12–14). In this study, we performed genetic analysis of nine colorectal PDNCs. Seven of these cases were associated with adenocarcinoma and/or adenoma (specimens 1–7); two cases had occurred as pure PDNC (specimens 8 and 9).

The specimens were also analyzed with the APC II marker, two specimens (Nos. 11 and 13) revealing no LOH and two specimens (Nos. 10 and 12) being noninformative. The results are summarized in Table 2.

DCC and p53 Gene Deletion

LOH analysis was performed with the DCC marker for the DCC gene. Five specimens (Nos. 1–3, 6, and 8) showed LOH, one specimen (No. 7) showed no LOH, and three specimens (Nos. 4, 5, and 9) were noninformative (Table 2, Fig. 2). In all cases with DCC gene deletion, DCC LOH was observed in the neuroendocrine carcinoma component. In specimens 1–3, there were identical allelic deletions of the DCC gene in the associated adenocarcinoma lesions. In specimen 6, loss of one DCC allele was observed in the adenoma and neuroendocrine carcinoma components, and loss of the opposite allele was seen in the adenocarcinoma component. Allelic loss of p53 was studied in six specimens. Five of these specimens were informative, and four of them showed LOH in the neuroendocrine carcinoma component (Table 2, Fig. 2). When present, the associated neoplastic processes showed loss of the same alleles (specimens 1 and 2).
mechanisms with adenocarcinoma. Therefore, this specimen provides evidence that differentiation into neuroendocrine carcinoma may occur at a relatively early stage of neuroendocrine carcinogenesis. Another specimen of pure neuroendocrine carcinoma (No. 9) also showed p53 LOH, but it was noninformative for the APC and DCC markers.

The findings of this study do not support the hypothesis of a nonepithelial endocrine cell as precursor for poorly differentiated colorectal neuroendocrine carcinoma. Instead, they suggest that, in the small number of specimens examined, the PDNC component and the adenocarcinoma component share the same cell of origin. It remains to be determined at which stage of carcinogenesis the pathways of differentiation separate. Thus, on the basis of the results presented, both the neuroendocrine carcinoma component and the adenoma and/or adenocarcinoma component may be derived from a multipotent epithelial stem cell that undergoes biphenotypic differentiation after carcinogenesis is initiated. It would also be conceivable that the neuroendocrine carcinoma component is a result of progression from adenocarcinoma into a PDNC phenotype. The progression to highly malignant neuroendocrine carcinoma may occur at an early stage during colorectal carcinogenesis. Subsequently, the adenocarcinoma component may be outgrown and remain undetectable even after thorough sampling of the entire tumor specimen.

In one specimen, we detected identical allelic loss of the APC gene not only in the primary lesion, but also in some of the regional lymph nodes that were involved by metastatic tumor (specimen 6). The detectability of potentially specific genetic changes from poorly differentiated metastatic carcinoma cells in regional colorectal lymph nodes by use of tissue microdissection may offer new diagnostic options to increase diagnostic acuity in undifferentiated metastatic tumor tissue, in which conventional histopathologic techniques fail to yield a specific diagnosis.

We further tested for allelic deletion of the APC gene in neuroendocrine carcinoid tumors (specimens 10–13). These tumors are believed to originate from neuroendocrine cells dispersed in the subepithelial stroma (15), possibly secondary to mucosal or submucosal persistence of fetal extraepithelial endocrine cells (16). The hypothetical neuroectodermal histogenesis of carcinoid tumors (15,16), however, has been challenged by other researchers who favor an endodermal origin of most endocrine cells of the digestive system (17). In our study, none of the carcinoid tumors showed allelic deletion of the APC gene. It is therefore likely that carcinoid tumors follow tumorigenesis pathways different from those of the highly malignant, poorly differentiated neuroendocrine carcinomas.

In summary, the results show that adenocarcinoma and PDNC share identical genetic changes of the adenoma–adenocarcinoma sequence. In association with these genetic changes, colorectal epithelium may give rise to adenoma, adenocarcinoma, and/or neuroendocrine tumor cells. Classic carcinoids do not appear to share these cancerogenetic pathways and, therefore, may represent genetically distinct neoplasms.

The classification of neuroendocrine tumors—in particular that of PDNCs—is highly controversial. In fact, the terms “neuroendocrine tumor” and “neuroendocrine carcinoma” are purely descriptive and are based on the presence of intracellular neurosecretory material. However, a classification concept as well as therapeutic strategies will ultimately be dependent on the recognition of the cellular origin of individual neuroendocrine tumors. By performing tissue microdissection and LOH analysis of adenocarcinoma cells and PDNC cells with markers corresponding to the “adenoma–adenocarcinoma sequence,” this study demonstrates for the first time a close genetic relationship of the morphologically heterogeneous carcinoma cells. Although mutation analysis of the APC, DCC, or p53 genes was not done in this study, the patterns of allelic loss within the different tumor components were highly consistent in all cases. In the future, the methodologic approach of this study may be applied to neuroendocrine tumors originating in other tissues.

The well-known aggressive biologic behavior of colorectal PDNCs is reflected by early dissemination of tumor cells from their site of origin. Poorly differentiated metastatic tumor—with or without neuroendocrine morphology—is commonly detected in lungs, liver, brain, or bone, prompting a thorough clinical search for the location of the primary tumor. In this setting, future studies will have to evaluate to what extent genetic analysis of poorly differentiated metastatic tissue with specific genetic markers provides valuable information about its site of origin.

References

(14) Schwartz AM, Orenstein JM. Small-cell undifferentiated carcinoma of the rectosigmoid
Risk of Urinary Tract Cancers Following Kidney or Ureter Stones

Wong-Ho Chow, Per Lindblad, Gloria Gridley, Olof Nyren, Joseph K. McLaughlin, Martha S. Linet, Gene A. Pennello, Hans-Olov Adami, Joseph F. Fraumeni, Jr.*

Background: A relationship has been suggested between kidney or ureter stones and the development of urinary tract cancers. In this study, a population-based cohort of patients hospitalized for kidney or ureter stones in Sweden was followed for up to 25 years to examine subsequent risks for developing renal cell, renal pelvis/ureter, or bladder cancer. Methods: Data from the national Swedish In-patient Register and the national Swedish Cancer Registry were linked to follow 61,144 patients who were hospitalized for kidney or ureter stones from 1965 through 1983. Standardized incidence ratios (SIRs) and 95% confidence intervals (CIs) were computed on the basis of nationwide cancer incidence rates, after adjustment for age, sex, and calendar year. Results: Risk of renal cell cancer was not elevated in this cohort. Significant excesses of renal pelvis/ureter cancer (SIR = 2.5; 95% CI = 1.8–3.3) and bladder cancer (SIR = 1.4; 95% CI = 1.3–1.6) were observed, but the SIRs for women were more than twice those for men. Risks varied little by age or duration of follow-up. Risks of renal pelvis/ureter cancer and bladder cancer among patients with an associated diagnosis of urinary tract infection were more than double those among patients without such infection, although the risks were significantly elevated in both groups. Conclusions: Individuals hospitalized for kidney or ureter stones are at increased risk of developing renal pelvis/ureter or bladder cancer, even beyond 10 years of follow-up. Chronic irritation and infection may play a role, since kidney or ureter stones were located on the same side of the body as the tumors in most patients with renal pelvis/ureter cancer evaluated in our study. [J Natl Cancer Inst 1997;89:1453–7]

Cancer of the renal pelvis has been linked to kidney stones in many case reports (1–5), attributed usually to the chronic irritation and infection associated with stones. This relationship has seldom been examined in case–control studies (6–8), although slightly elevated risks have been suggested. On the other hand, renal cell cancer (tumors arising in the renal parenchyma) has rarely been linked to kidney stones in case reports (9), although an association has been suggested in a few case–control studies (10–13). The relationship between kidney or ureter stones and bladder cancer also is unclear (14,15), although urinary tract infection is generally considered to be a risk factor (16–18).

In this study, a population-based cohort of patients hospitalized for kidney or ureter stones in Sweden was followed for up to 25 years through record linkage to the nationwide tumor registry to examine subsequent risks for the development of cancers of the renal parenchyma, renal pelvis/ureter, and bladder. To assess whether the tumors are related to chronic irritation produced by the stones or to characteristics of the urine associated with stone pathogenesis, we reviewed the medical records to determine the laterality of the tumors and the stones.

Patients and Methods

The data used for this study and the method of patient follow-up have been described in detail else-