Distinct Pattern of ret Oncogene Rearrangements in Morphological Variants of Radiation-induced and Sporadic Thyroid Papillary Carcinomas in Children

Yuri E. Nikiforov, Jon M. Rowland, Kevin E. Bove, Hector Monforte-Munoz, and James A. Fagin

Division of Endocrinology, University of Cincinnati College of Medicine, Cincinnati, Ohio 45267-0547 (Y. E. N., J. A. F.); Department of Pathology, Children's Hospital Los Angeles, Los Angeles, California 90027 (J. M. R., H. M.-M.); and Department of Pathology, Children's Hospital Medical Center, Cincinnati, Ohio 45229 (K. E. B.)

ABSTRACT

In this study, we compare the morphological and genetic characteristics of 38 post-Chernobyl thyroid papillary carcinomas from Belarusian children 5–18 years old with those of 23 sporadic papillary carcinomas from the same age children without history of radiation exposure from Los Angeles and Cincinnati. Among radiation-induced tumors, solid variant of papillary carcinoma was found in 37%, follicular in 29%, typical papillary in 18%, and mixed and diffuse sclerosing variants in 8% each. In the sporadic group, a typical papillary pattern was prevalent in 70%, follicular in 17%, diffuse sclerosing variant in 9%, and solid in 4%. In both groups, the prevalence of ret rearrangements was high, but the frequency of specific types of rearrangement was significantly different. Among radiation-induced tumors, ret/PTC3 was found in 58%, ret/PTC2 in 16%, and ret/PTC1 in 3%, whereas among sporadic tumors, ret/PTC1 was found in 47% (P < 0.05), and ret/PTC3 was found in 18% (P = 0.01). The morphological variants of papillary carcinoma showed different prevalence of the specific types of ret rearrangement. Seventy-nine percent of solid variant tumors had ret/PTC3, whereas only 7% had ret/PTC1 (P = 0.0007). Among typical papillary tumors, ret/PTC1 was found in 38%, ret/PTC3 in 19%, and ret/PTC2 in 5%. Thus, ret rearrangements are highly prevalent in pediatric papillary carcinomas from children exposed to radiation and in those occurring sporadically. However, the types of ret/PTC vary between these two populations, with ret/PTC3 present more commonly in post-Chernobyl tumors. Furthermore, solid variants have a high prevalence of ret/PTC3, whereas typical papillary carcinomas do not, suggesting that the different types of ret rearrangement confer neoplastic thyroid cells with distinct phenotypic properties.

INTRODUCTION

Thyroid cancer in children exposed to radiation as a result of the Chernobyl nuclear accident in April, 1986 is now a widely accepted paradigm of radiation-induced neoplasia. A sharp increase in the incidence of pediatric thyroid carcinoma was noted as soon as 4 years after the accident (1). Thus far, several hundred cases have been reported in children living in the contaminated areas of Belarus, Ukraine, and western regions of Russia, resulting in up to a 100-fold increased annual incidence of childhood thyroid carcinoma compared to that prior to 1986 (2, 3).

The vast majority of these tumors are thyroid carcinomas of the papillary type. A detailed morphological analysis of 84 cases from Belarus showed that solid and follicular variants of papillary carcinoma were prevalent in these tumors (4). Spontaneous papillary thyroid carcinomas are extremely rare in children, and to our knowledge their morphological variants have not been characterized in detail.

Our understanding of the genetic events associated with radiation-induced thyroid cancer in general, and of post-Chernobyl tumors in particular, is far from complete. ras oncogene mutations, which are found in 18–62% of papillary carcinomas in the general population, are not observed at all in these tumors (5, 6). Mutations of the p53 gene, which are common in sporadic undifferentiated and poorly differentiated thyroid carcinomas (7, 8), have a very low prevalence in the Chernobyl population (5, 6), in spite of the fact that many papillary carcinomas in the latter population have a solid growth pattern, indicative of a less differentiated phenotype.

Recently, two studies of a small series of post-Chernobyl papillary thyroid carcinomas reported a 67% prevalence of the ret gene rearrangements (9, 10). ret rearrangements are formed by the fusion of the intracellular tyrosine kinase domain of the gene with different 5' gene fragments, resulting in inappropriate constitutive expression of the truncated tyrosine kinase domain of the receptor. The authors proposed that this genetic event might reflect a radiation origin of these tumors. Indeed, the incidence of ret alterations found in pediatric post-Chernobyl tumors is much higher than that reported previously in the general (mostly adult) population, where three types of ret rearrangements, ret/PTC1, ret/PTC2, and ret/PTC3 have been detected in up to 34% of papillary thyroid carcinomas (data summarized in Ref. 11). In addition, the induction of ret/PTC1 rearrangement has been reported after high dose X-ray irradiation in vitro (12). However, a recently published study demonstrates a similarly high incidence of ret/PTC rearrangements in spontaneous thyroid carcinomas in Italian children but not in adults, suggesting that this might be an age-specific, rather than radiation-specific, event (13).

To clarify the role of ret oncogene alterations in radiation-induced carcinogenesis in the thyroid gland and to compare the morphology of radiation-induced and spontaneous thyroid cancers in children, we studied a large series of post-Chernobyl pediatric papillary thyroid carcinomas and compared them with a group of pediatric tumors without a history of radiation exposure from two different areas in the United States.

MATERIALS AND METHODS

Patient Population. Thirty-eight cases of thyroid papillary carcinoma from Belarusian children 5–18 years of age who lived in the areas contaminated as a result of the Chernobyl nuclear accident were studied. These cases were selected from a large consecutive series of thyroid tumors in children that underwent surgery at the Thyroid Tumor Center in Minsk in 1991–1992 based on the availability of RNA extracted from paraffin-embedded tissue of sufficient integrity to allow genetic analysis. The morphological and epidemiological features of these tumors have been described previously (4, 14). To perform a comparative analysis of radiation-induced and sporadic pediatric thyroid tumors, records of all cases of thyroid carcinoma in children up to 18 years old were obtained from the files of the Department of Pathology at Children's Hospital Los Angeles (Los Angeles, CA) and the Department of Pathology at Children's Hospital Medical Center (Cincinnati, OH). Fourteen primary cases of papillary carcinoma were found in Los Angeles since 1974 and 10 cases in Cincinnati since 1982. The medical records of each patient were reviewed for radiation history. One patient from Cincinnati had received X-ray therapy in a dose of 1800 rads to the brain area for acute lymphoblastic leukemia 8 years prior to removal of thyroid carcinoma. The latter case was eliminated from further analysis. Altogether, 23 spontaneous papillary thyroid carcinomas from children 5–18 years of age were studied.
Histology. Histological slides from primary thyroid tumors stained by H&E were reviewed by at least two pathologists (Y. E. N., J. M. R., and H. M.-M.; or Y. E. N. and K. E. B.) to confirm the diagnoses and subclassify the variants of papillary carcinomas. Simultaneously, the sections containing 70-100% of tumor from lymph node metastasis or primary nodules were selected for RNA extraction from the corresponding paraffin blocks.

Genetic Analysis. In all cases, RNA was extracted from paraffin-embedded tissue as reported previously (15, 16). In addition, in five cases from Cincinnati, RNA was obtained from frozen tissue as described by Chomczynski and Sacchi (17). After reverse transcription at 42°C by Superscript reverse transcriptase (BRL) using a random hexanucleotide mixture as a primer, cDNA was first tested to ensure that the integrity of RNA was sufficient for analysis. For this purpose, a 236-bp sequence of the c-N-ras cDNA was amplified with two sets of intron-spanning primers (Table 1). The cDNAs of the tumors capable of PCR amplification were then further analyzed. To screen for ret mRNA expression, we first coamplified using two sets of intron-spanning primers (Table 1). The cDNAs of the tumors demonstrating preferential expression of the TK domain were considered as suspicious for having ret rearrangements. Nevertheless, all tumor cDNAs were screened with primers bracketing chimeric sequences corresponding to the rearrangements of ret/PTC1, ret/PTC2, and ret/PTC3 types (Table 1). For each PCR, 2 μl of reverse transcribed mixture were amplified with 10 pmol of each primer, 200 μM deoxynucleotide triphosphates, 10 mM Tris-HCl (pH 9.0 at 25°C), 50 mM KCl, 1% Triton X-100, 1.5 mM MgCl₂, and 1 unit of Taq DNA polymerase (Promega Corp., Madison, WI) in a final volume of 30 μl. Thirty-five cycles of denaturation (94°C for 1 min), annealing (55°C-63°C for 1 min), and extension (72°C for 1.5-2 min) were conducted on an automated heat block (DNA thermal cycler; Perkin-Elmer, Norwalk, CT). Positive controls for amplification included RNA samples from a medullary thyroid carcinoma with constitutive expression of wild-type c-ret (for amplification of ret TK and EC domains), from the TPC-1 cell line with a ret/PTC1 rearrangement (18), and cloned vectors containing ret/PTC2 and ret/PTC3 rearranged genes kindly provided by Dr. S. M. Jiang (Ohio State University, Columbus, OH).

Ten μl of PCR product were electrophoresed in a 1.5% agarose gel and blotted to a nylon membrane. Each filter was then hybridized with the corresponding specific probe (Table 1) for 16 h at 42°C, washed, and exposed for autoradiography for 4–16 h.

Statistical Analysis. A χ² method was used to test heterogeneity among the various groupings in the radiation-induced and sporadic sets. Because many groupings had a small number of observations, the test of two proportions with double-sided confidence limits and the Yates correction was performed to test whether specific proportions were different between two groupings. Alternatively, the two-tailed Fisher exact test was used for smaller sample sizes (19). Two values were considered significantly different when the probability of P was less than 0.05.

RESULTS

Table 1 Primers and probes used for the screening

<table>
<thead>
<tr>
<th>Size (bp)</th>
<th>Primer sequences (5'-3', a-sense, b-antisense)</th>
<th>Nucleotide positions</th>
<th>Probes for hybridization (5'-3')</th>
</tr>
</thead>
<tbody>
<tr>
<td>c-ras</td>
<td>a-AGTAGCTGTGAAACACTGTG</td>
<td>727-746</td>
<td>CAATCTTTGGTTTATGATGTGTA</td>
</tr>
<tr>
<td></td>
<td>b-AGGAAACCTTGGCTGGTTGCCT</td>
<td>943-962</td>
<td></td>
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<tr>
<td>c-ret, TK</td>
<td>a-GAGACCCAATGGCTGGAAAGATTCCAGAGTTGA</td>
<td>2654-2677</td>
<td>ACGAAAGTAGTTGCTAAGGCTT</td>
</tr>
<tr>
<td></td>
<td>b-CCGCCCTAGGAAATCCAGAGGTGTT</td>
<td>2705-2728</td>
<td></td>
</tr>
<tr>
<td>c-ret, EC</td>
<td>a-CCGCCCTAGGAAATCCAGAGGTGTT</td>
<td>1353-1374</td>
<td>GTAAACAGGAGGGGTCATATG</td>
</tr>
<tr>
<td></td>
<td>b-CCGCCCTAGGAAATCCAGAGGTGTT</td>
<td>1513-1535</td>
<td></td>
</tr>
<tr>
<td>ret/PTC1</td>
<td>a-GATCAGGACCTCAAACTGTA</td>
<td>279-298</td>
<td>GCACTGAGGAGGAGGACCCA</td>
</tr>
<tr>
<td></td>
<td>b-GTTGTCCTGAGACTACCTTTTC</td>
<td>425-443</td>
<td></td>
</tr>
<tr>
<td>ret/PTC2</td>
<td>a-GCTTGAGGACTGTTGTTT</td>
<td>605-626</td>
<td>GACCGAGACGCTATGAGAATC</td>
</tr>
<tr>
<td></td>
<td>b-GTTGTCCTGAGACTACCTTTTC</td>
<td>788-806</td>
<td></td>
</tr>
<tr>
<td>ret/PTC3</td>
<td>a-AGGCAACACTGCGACAGG</td>
<td>687-704</td>
<td>GTTGCGTGCTGCGATGTAAGAGA</td>
</tr>
<tr>
<td></td>
<td>b-CTTCAGGACCTTCCAGCG</td>
<td>911-928</td>
<td></td>
</tr>
</tbody>
</table>

* Nucleotide positions of the primers are based on the sequences deposited in GenBank: c-N-ras (accession no. X02751), c-ret (accession no. X12949), ret/PTC1 (accession no. M31213), ret/PTC2 (accession no. L03357), and ret/PTC3 (accession no. S71225).

Ten pi of PCR product were electrophoresed in a 1.5% agarose gel and stained with ethidium bromide. Positive bands were excised and purified with a MaxiPrep purification kit (Bio-Rad, Hercules, CA). The cDNA samples were then sequenced with specific primers using the BigDyeTM Terminator Cycle Sequencing Kit (Applied Biosystems, Foster City, CA) and analyzed with an automated DNA sequencer (Perkin-Elmer). The sequences were compared with cDNA sequences available in GenBank.

RESULTS

Epidemiological and Morphological Characteristics. The age of children in both groups ranged from 5 to 18 years. The mean age was 11.2 years among post-Chernobyl tumors, and 13.7 years among spontaneous thyroid carcinomas. In the former group, there were 18 girls and 20 boys, resulting in a female: male ratio of 0.9:1. In the latter group, there were 20 girls and 3 boys with a sex ratio of 6.6:1 (P < 0.01). Morphologically, papillary carcinomas were classified according to the prevalent growth pattern in the primary tumor nodules as either typical papillary, follicular, or solid variant (Fig. 1). Typical papillary carcinomas were composed of papillae with a central fibrovascular core covered by neoplastic epithelial cells. The follicular variant tumors contained predominantly follicles, which varied in size and content of colloid, and were lined by epithelium with cytological features of papillary carcinoma. The solid variant was composed exclusively or predominantly by sheets of neoplastic cells surrounding by a variable amount of fibrotic stroma; the typical nuclear features of papillary carcinoma were commonly retained. Mixed variant was diagnosed in cases when the tumor nodule displayed an almost equal prevalence of any two or all three patterns of growth. In addition, tumors were classified as diffuse sclerosing variant based on a diffuse type of growth without a distinguishable solitary nodule, presence of severe fibrosis, dense lymphocytic infiltration, and areas of squamous metaplasia (20). The prevalence of morphological variants in both groups are summarized in Table 2. The distribution of histological phenotypes was found to be significantly different between radiation-induced and sporadic tumors (χ² test, P < 0.001). Typical papillary carcinoma was significantly more prevalent among sporadic tumors (test of proportions, P < 0.001), whereas solid variant tumors were more common among the exposed children (Fisher’s Exact test, P = 0.006).

Molecular Genetic Analysis. Of 38 radiation-induced tumors, 33 (87%) showed preferential or exclusive expression of the TK domain as opposed to the EC domain of c-ret, indicating the possible occurrence of rearrangements with a breakpoint somewhere between these two regions (Fig. 2A). All of these positive cases were screened for the three known types of ret/PTC rearrangements. ret/PTC1 type was identified in 6 cases (16%), ret/PTC2 in 1 case (3%), and ret/PTC3 was found in 22 cases (58%; Fig. 2B). In 4 cases with strong expression of TK domain (cases R25, R32, R33, and R35), none of the known types of ret rearrangement was identified, in spite of the fact that the experiment was replicated twice with fresh preparations of tumor RNA. The mean age at the time of radiation exposure was 4.3 years among those with ret/PTC3, 4.2 years among those who had ret/PTC2, and 11.2 years among post-Chernobyl tumors.
mors did not correlate significantly with patients' sex, despite a dramatic difference in sex ratio between the two groups as a whole. On the other hand, there was a close correspondence between the type of ret/PTC rearrangement and the morphological characteristics of the tumors (Table 4). Most notably, solid variant neoplasms had a very high prevalence of ret/PTC3 rearrangement, whereas typical papillary carcinomas did not (Fisher's Exact test, $P = 0.0007$).

**DISCUSSION**

To our knowledge, this is the largest comparative analysis of radiation-induced and sporadic thyroid carcinomas in children that demonstrates clear differences in some epidemiological characteristics, morphology, and types of the ret oncogene alteration between these two groups of pediatric neoplasms. In addition, this is the first study documenting an association between different types of ret rearrangement and distinct phenotypic variants of papillary thyroid carcinoma.

There was a significant difference in sex distribution between both groups, with an almost equal female: male ratio among radiation-induced tumors and a dramatic female predominance among sporadic cases. Morphological analysis indicated that solid and follicular variants of papillary carcinoma were more prevalent in radiation-induced tumors. This was particularly obvious for the solid variant, which constituted 37% of radiation-induced but only 4% of sporadic tumors. In addition, three cases of mixed variant tumors (composed of equal portions of solid and follicular pattern in two cases, and of a mixture of solid, follicular, and typical papillary patterns in one case) were found only in the radiation-induced group, making the predominance of solid growth pattern in this group even higher. The solid variant of papillary carcinoma, which is a rare finding in either children or in the adult population (21), is poorly characterized from the point of view of biological behavior and patient prognosis but is generally considered to be a more aggressive form of the disease. In contrast to radiation-induced neoplasms, tumors displaying the typical papillary pattern were characteristic of the sporadic group. In this respect, sporadic pediatric papillary carcinomas are similar to papillary carcinomas in the adult population.

ret rearrangements were highly prevalent in both groups. However, the prevalence of specific types of rearrangement was markedly different; ret/PTC1 was the dominant form in sporadic tumors, and ret/PTC3 was the dominant form in radiation-induced neoplasms. Arguably, pediatric tumors from the United States are not the best control group for comparison with tumors found in Belarusian children. However, sporadic thyroid carcinomas were collected from children residing in two different areas in the United States. In addition, similar data on predominance of ret/PTC1 over ret/PTC3 types of rearrangement in sporadic pediatric thyroid carcinomas have been reported in Italian children and adolescents younger than 19 years of age (13). In contrast, the predominance of ret/PTC3 in post-Chernobyl pediatric papillary carcinomas has been reported before in the series of 6 and 12 cases (9, 10).

The histological variants of papillary carcinoma exhibited strong correspondence with the type of ret rearrangement. Thus, among post-Chernobyl carcinomas, solid variant tumors exhibited a striking

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**Table 2 Prevalence of morphological variants of papillary carcinoma among radiation-induced and sporadic pediatric thyroid tumors**

<table>
<thead>
<tr>
<th>Variants of papillary carcinoma</th>
<th>Number of cases</th>
<th>Solid</th>
<th>Follicular</th>
<th>Typical papillary</th>
<th>Mixed</th>
<th>Diffuse sclerosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiation-induced</td>
<td>38 (100%)</td>
<td>14 (37%)$^a$</td>
<td>11 (29%)</td>
<td>7 (18%)</td>
<td>3 (8%)</td>
<td>3 (8%)</td>
</tr>
<tr>
<td>Sporadic</td>
<td>23 (100%)</td>
<td>1 (4%)</td>
<td>4 (17%)</td>
<td>16 (70%)$^b$</td>
<td>0</td>
<td>2 (9%)</td>
</tr>
</tbody>
</table>

$^a$ $P = 0.006$ in comparison with the prevalence of solid variant in sporadic tumors.

$^b$ $P < 0.001$ in comparison with the prevalence of typical papillary variant in radiation-induced tumors.

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![Fig. 1. Morphology of the major variants of papillary thyroid carcinomas according to the prevalent type of growth: a, typical papillary carcinoma; b, follicular variant; and c, solid variant. H&E staining. ×180.](image-url)
cinomas both in radiation-induced and sporadic groups. Almost one third of carcinomas with typical papillary growth had no detectable rearrangements of ret. These data indicate that different types of ret rearrangement are associated with distinct phenotypes of papillary carcinoma. This observation was not expected, because all types of ret rearrangement lead to the inappropriate expression of the intracellular domain of the ret receptor. This is thought to be a major mechanism of thyroid cell transformation (22, 23). The three types are formed by the fusion of the TK domain of ret to different 5' partners. ret/PTC1 is formed by a paracentric inversion of the long arm of chromosome 10, leading to fusion with a gene named H4/D10S170 (24). ret/PTC3 is also a result of an intrachromosomal rearrangement and is formed by the fusion with the RFG/ELE1 gene also located on chromosome 10 (25, 26). ret/PTC2 is formed by a reciprocal translocation between chromosomes 10 and 17, resulting in the fusion of the TK domain of c-ret with 5' terminal sequence derived from the regulatory subunit of Ria cAMP-dependent protein kinase A (27). In all cases, fusion points are located within the intron bracketed by the transmembrane domain and the TK region of ret. The truncated fragment of ret lacks the transmembrane domain and has been shown to be located within the cytosol (28). The expression of this chimeric product is driven by the respective promoters of the genes upstream of the rearrangement. The contrasting phenotypes reported here between tumors harboring ret/PTC1 and ret/PTC3 translocation may be due to unique effects of the sequences upstream of the breakpoint or to the levels of activity of the ret/PTC1 and ret/PTC3 promoters, which may result in important differences in the absolute amounts of the truncated ret mRNA and protein. These data, therefore, point to important structural differences between the various rearranged forms of ret, which are worthy of further study.

Table 3 Prevalence of ret rearrangements in radiation-induced and sporadic pediatric thyroid tumors

| TK positive | ret/PTC1 | ret/PTC2 | ret/PTC3 | Novel ret/PTC |
|-------------|---------|---------|---------|---------------|-----------------|
| Radiation-induced | 6 (16%) | 1 (3%) | 22 (58%) | 4 (10%) | 5 (13%) |
| Sporadic | 8 (47%) | 0 | 3 (18%) | 1 (6%) | 5 (29%) |

a P = 0.01 in comparison with the prevalence of ret/PTC3 in sporadic tumors.
b P < 0.05 in comparison with the prevalence of ret/PTC1 in radiation-induced tumors.

Fig. 2. Screening of radiation-induced tumors for ret gene rearrangements. cDNA was amplified with the indicated primers followed by Southern blotting and hybridization with specific probes (Table 1). A, amplification of the fragments corresponding to the TK and EC domains of c-ret. Positive control (Pos. C.) is medullary thyroid carcinoma with expression of wild-type, full-length c-ret mRNA. Negative control (Neg. C.) is in the absence of template. Tumors demonstrating disproportionate expression of TK as opposed to EC domain were considered to be positive for ret rearrangement. B, amplification of ret/PTC1, ret/PTC2, and ret/PTC3 in each tumor sample, positive controls (indicated in "Materials and Methods"), and negative control. ret/PTC1, ret/PTC2, or ret/PTC3 were found in all TK-positive cases except for R25, R32, R33, and R35. As expected, tumor samples that were negative for expression of TK (R10, R16, R34, R36, and R38) did not show evidence of either ret/PTC1, ret/PTC2, or ret/PTC3.

Fig. 3. Screening of sporadic tumors for ret gene rearrangements. A, amplification of the fragments corresponding to the TK and EC domains of c-ret. Tumors demonstrating disproportionate expression of TK as opposed to the EC domain were considered to be positive for ret rearrangement. Negative cases had no expression of either the TK or EC domain of ret (54, 56, 57, and 512) or exhibited low abundance of both fragments (511) proportional to the expression of TK and EC in the C-cell tumor (positive control; Pos. C.). In B, ret/PTC1 or ret/PTC3 rearrangements were found in all cases positive for TK expression except for case 514.
F. Five of the cases reported here had clear evidence of preferential expression of the TK fragment of ret, which was not due to either ret/PTC1, ret/PTC2, or ret/PTC3, suggesting that it may have resulted from novel forms of ret rearrangement. While this report was in preparation, a subtype of ret/PTC3 containing an additional 93 bp was reported and termed ret/PTC4 (29). However, it appears that at best only one of the five tumors may be explained by ret/PTC4 (data not shown), indicating that additional rearrangements of ret are present in tumors from this pediatric population.

The prevalence of ret rearrangements found in both pediatric groups is much higher than in adults. This invites the speculation that almost all thyroid carcinomas in children may be radiation induced. If this were the case, the differences observed in this study may be due to the fact that in the documented radiation-induced cases, the high-dose exposure led primarily to ret/PTC3 types of rearrangement and a solid growth pattern. The so-called sporadic tumors may have also been induced by radiation but by inadvertent exposure to lower doses that led to tumor development in children with a higher susceptibility to radiation-induced DNA damage, and are characterized primarily by ret/PTC1 types of rearrangement and a typical papillary growth pattern. Alternatively, only post-Chernobyl tumors may be truly radiation induced, and the high prevalence of ret rearrangements in the sporadic cases are due to alternative mechanisms of tumor initiation. Regardless of the manner in which these mutations take place, this study shows that the different types of ret rearrangements result in distinct morphological tumor phenotypes and possibly in cancers with different biological behaviors.

ACKNOWLEDGMENTS

We are grateful to Dr. Nobuo Satoh (Kanazawa University, Japan) for providing the TPC-1 cell line, to Dr. S. M. Jiang (Ohio State University, Columbus, OH) for providing clones of ret/PTC2 and ret/PTC3 rearrangements, and to Dr. H. Kalkwarf (University of Cincinnati) for advice on statistical analysis.

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