Abstract. The study investigated an association between the germline polymorphism at TP53 codon 72 and the development of papillary thyroid cancer (PTC) following exposure to radiation from the Chernobyl accident. TP53 genotype was examined in 48 pediatric/adolescent (age at diagnosis <18 years) and 68 adult post-Chernobyl patient with PTC, 53 adult patients with sporadic PTC and 313 healthy individuals from Russian-Ukrainian population. In addition, we evaluated loss of heterozygosity for TP53 and the allele expression ratio. The genotype of the patients was correlated with clinico-pathological data. Arg TP53 homozygotes were found to be significantly underrepresented among adults with post-Chernobyl PTC, but not in children and adolescents when compared with sporadic PTC cases and the general population. In the tumors, cell transformation did not lead to allelic loss or biased TP53 allele expression in heterozygous individuals. None of TP53 genotypes specifically associated with tumor stage and morphology, however there were particular correlations with lymph node status in certain age groups of radiation-associated cases not seen in sporadic PTCs. The findings suggest TP53 allele combinations other than Arg/Arg may contribute to the risk of development of PTC in individuals exposed to radiation during their late childhood, adolescence or in young adulthood.

Introduction

p53 protein plays a key role in a variety of cellular processes mediating cell cycle arrest, apoptosis, senescence and DNA repair. Somatic mutation of TP53 is known to be one of the most frequent genetic alterations in cancer being detected in about 50% of human malignancies (1). The mutation may result in compromised protein function and potentially contribute to tumor growth and genomic instability. p53 levels in a cell may change dramatically following exposure to stress e.g. ionizing or UV radiation, hypoxia, heat shock, growth factor withdrawal, oncogene activation and exposure to cytotoxic drugs (2,3). Elevation of p53 intracellular content is largely attributed to increased protein stability which is achieved by multiple posttranslational modifications resulting in its attenuated proteosomal degradation. p53-regulated apoptosis in insulted cells may be exerted both by transcription-dependent and transcription-independent mechanisms. With regard to the latter, after hypoxia and DNA damage, p53 has been shown to be able to translocate to mitochondria where it can interact with and impair anti-apoptotic Bcl-2 and BCL-XL proteins (4,5). At least in part, p53 translocation to mitochondria is dependent on the p53 variant structure. It has been demonstrated that p53 with an arginine residue at amino acid position 72 (72Arg) reaches the organelle and induces apoptosis through cytochrome c release more efficiently than the p53 72Pro variant (6). The two p53 isoforms with either 72Arg or 72Pro are the result of a common polymorphism in exon 4 of TP53 gene (encoded by CGC and CCC codons, respectively). This single nucleotide polymorphism occurs in the fragment of the gene encoding a
proline-rich region (residues 61-94) of the protein which is essential for apoptosis and growth suppression, but not for transactivation of the p53 target genes (7).

The p53 72Arg/Pro polymorphism has been, sometimes controversially, associated with various human malignancies, such as breast (8,9), cervical (10,11) and lung cancer (12), cutaneous squamous cell carcinoma in renal transplant patients (13) and sporadic thyroid cancer (14,15). No significant relationship between 72Arg/Pro p53 polymorphism has been found in hepatocellular (16), ovarian (17), brain (18), cervical (19-21), colorectal (9) and other digestive tract cancers (22). Thus, it is likely that in several types of human malignancies not only mutated p53, but also functional p53 variants may affect the tumor development.

Thyroid gland is well known to be an organ particularly vulnerable to radiation (23). After the Chernobyl accident in 1986, incidence of papillary thyroid cancer (PTC) sharply increased especially in the individuals exposed at the young age (24,25). It is believed that TP53 mutation does not associate with well-differentiated thyroid cancer (such as PTC) and therefore cannot serve as a pathognomonic marker of radiation-induced disease. Indeed, TP53 mutations in both radiation-induced and sporadic PTCs were shown to be infrequent. Only 1-3% of radiation-induced (26-28) and comparable proportion of spontaneous PTCs have been reported to harbor TP53 alterations (29). On the other hand, normal thyrocytes, similarly to many other types of cells, show a dose-dependent increase and time-dependent changes of p53 level after radiation exposure accompanied by DNA repair in vitro (30).

Given that p53 is involved in radiation response of human thyrocytes and there is a difference in biological behavior between p53 polymorphic variants, we set out the study to determine TP53 allelic form prevalence in radiation-associated post-Chernobyl PTCs and to compare it to that in sporadic thyroid cancer and an ethnically matched general population to address a hitherto unanswered question whether p53 amino acid 72 polymorphism may be relevant to the risk of development of radiation-induced PTC.

Materials and methods

Patients and control subjects. The study included DNA samples from 169 PTC patients from Ukraine and Russia and 313 ethnically matched healthy individuals. Among the thyroid cancer cases, we distinguished two different etiopathogenic types, the radiation-associated PTCs (thyroid cancer in residents of the territories of Ukraine and Russia contaminated with radioisotopes after the Chernobyl accident, n=116) and sporadic PTCs (no history of radiation exposure, n=53). The radiation-associated PTCs included 97 post-Chernobyl cases from Ukraine and Russia and 313 patients whose age at the moment of exposure to radioiodine after the Chernobyl accident (April, 1986) was 0-18 years and additionally 19 PTC cases from adult female patients whose age at the time of the Chernobyl accident was 18-30 years. Radiation risks for thyroid cancer have been recently validated in the latter subgroup of the population exposed to radionuclides after the Chernobyl fall out (31) therefore such cases were combined in this study with those traditionally assigned radiation-induced post-Chernobyl PTCs (aged at exposure 0-18 years). In the radiation-associated group, there were 48 pediatric/adolescent cases (patients aged <18 years at diagnosis) and 68 adult PTCs. All patients from both radiation-associated and sporadic PTC groups were operated on for thyroid cancer in 1996-2003. The control group was composed of Caucasian volunteers, residents of Russia, who agreed to anonymously donate a buccal specimen with only gender and age at sampling recorded. Initially approached 454 individuals, donated 321 specimens (70.7%, response rate; in 8 cases DNA extraction failed). Demographic and clinicopathological characteristics of the subjects included in the study are listed in Table I.

Specimens. Snap-frozen thyroid tumor and matched normal tissue specimens were collected from the patients in Medical Radiological Research Center of Russian Academy of Medical Sciences (MRRC RAMS, Obninsk, Russia) with appropriate informed consent (30 of 97 post-Chernobyl PTCs and 19 PTCs in female patients described above in the radiation-associated group, and all sporadic PTCs).

DNA samples from post-Chernobyl Ukrainian radiation-associated PTCs (67 cases, ready to use DNA from the tumor and normal thyroid tissue) were provided by the Chernobyl Tissue Bank (URL, http://www.chernobyltissuebank.com/).

DNA was purified from frozen thyroid tissues and buccal swabs using a standard proteinase K/phenol-chloroform protocol and BuccaAmp DNA Extraction Kit (Epicentre, Madison, WI, USA), respectively. The study was approved by the respective ethics boards of Nagasaki University and MRRC RAMS.

Arg72Pro polymorphism by real-time PCR allelic discrimination assay. To detect the polymorphism, we designed two primers, TP53Ex4F (5'-CGTCCCCAACGCAATGGATGAG-3') and TP53Ex4R (5'-CGTGGCCCC-TAMRA-3') specific to the alleles encoding 72Arg and 72Pro, respectively. The 25 μl reaction mixture contained 10-50 ng of DNA as a template, 12.5 μl of each primer and 400 nM of each probe. The reactions were performed in duplicates in an ABI PRISM 7700 Sequence Detector (Applied Biosystems, USA). PCR conditions were as follows: 50°C for 2 min, 95°C for 10 min, then 35 cycles of 95°C for 15 sec and 61°C for 1 min.

Direct sequencing. For PCR amplification and direct sequencing of the fragment of TP53 exon 4, two primers were used: forward 5'-TCCCCCTTGCCGTCCCAAA-3' (pos. 522-539) and reverse 5'-CGTGGCCCCCGTGACAGCCTT-3' (pos. 783-800). The reaction was performed in a 25 μl mixture containing 50-100 ng of DNA template, 200 nM of each primer, 2.5 μl of 10X PCR Gold Buffer, 0.8 mM of dNTPs, 1.5 mM of MgCl₂ and 1.25 units of AmpliTaq Gold DNA Polymerase (all reagents from Applied Biosystems, USA). PCR conditions were as follows: 95°C for 10 min, then 35 cycles of...
95˚C for 30 sec, 54˚C for 30 sec, 72˚C for 30 sec and finally 10 min at 72˚C. After visualization in a 1.5% TAE agarose gel, remaining PCR products (5 μl) were treated with ExoSAP-IT PCR clean-up reagent (USB Corp., USA) and sequenced in both directions on an ABI 3100 automated sequencer (Applied Biosystems, USA) using Big Dye Terminator v3.1 Cycle Sequencing reagents (Applied Biosystems, Warrington, UK) and either forward or reverse primer.

Expression levels of TP53 allelic variants. RNA was extracted from frozen tumor and normal thyroid tissues with Isogen reagent (Nippon Gene, Tokyo, Japan) according to the manufacturer’s protocol. To avoid DNA contamination, 10 μg of total RNA was treated with 2.5 units of RNase-free DNase I (Takara, Tokyo, Japan) for 30 min at 37˚C, heated at 70˚C for 30 min and recovered with Isogen. First strand cDNA was synthesized from 2 μg of DNase I-treated RNA in the presence of random hexamers and MuLV reverse transcriptase (Applied Biosystems, Foster City, CA, USA). Efficacy of DNase I treatment was assured by the absence of a 113 bp PCR product after an extensive amplification (40 cycles) of a portion of human TG gene (encodes thyroglobulin) using forward primer located in intron 10 of the gene (5’-GTGAGGGCACACATGCTTCAT-3’, pos. 61-81 in the sequence available under GenBank accession number X06070) and reverse primer located in TG exon 11 (5’-CGGAGCTTTGCCTTCACA-3’, pos. 154-173) (data not shown). Thereafter, the relative expression of TP53 allelic forms was evaluated in heterozygous specimens by real-time PCR allelic discrimination assay as described above. For calibration, DNA templates with varying proportion (0-100%) of either variant allele made by combining the corresponding homozygous DNA samples were used.

Tumor morphology and clinicopathological data. All tumors were diagnosed as PTCs according to the World Health Organization. The clinicopathological parameters are presented in Table I.

Table I. Summary of PTC patients and controls included in the study.

<table>
<thead>
<tr>
<th></th>
<th>Radiation-associated PTC, (n=116)</th>
<th>Sporadic PTC (n=53)</th>
<th>Control Population (n=313)</th>
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<tr>
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<td>Pediatric/adolescent (n=48)</td>
<td>Adult (n=68)</td>
<td>Total (n=116)</td>
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<td>Gender, F/M (ratio)</td>
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<td>55/13 (4.2:1)</td>
<td>86/30 (2.9:1)</td>
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<td>(25)</td>
<td>(21)</td>
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<td>Age at exposure, years,</td>
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<td>range (median)</td>
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<td>(8)</td>
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<tr>
<td>Period of latency, years,</td>
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<td>11.2-17.5</td>
<td>10.0-17.5</td>
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<tr>
<td>range (median)</td>
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<td>(14)</td>
<td>(14)</td>
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<td>Tumor morphology</td>
<td></td>
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<tr>
<td>Solid</td>
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<td>5</td>
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<tr>
<td>Positive</td>
<td>4</td>
<td>5</td>
<td>9</td>
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</tbody>
</table>

*Age was recorded at the moment of sampling. *NA, not applicable. *Morphology is stratified for major histological component of the tumor; data were available for 47 pediatric/adolescent and 68 adult radiation-associated PTCs, and 51 sporadic PTCs. *Tumor staging was performed according to De Groot et al (33).
Organization histological typing of thyroid tumors classification (32). Morphological characteristics were provided by experienced pathologists (A.Yu.A., E.F.L. and T.I.B.) with respect to the tumor histological variant. Approximately a half of the tumors included in the study had mixed architecture, therefore the major component, i.e. papillary, follicular or solid, was considered for further analysis for simplicity. Information on tumor extent and metastatic lesions was retrieved from medical records. Tumor staging (clinical class) was performed as described (33).

Statistical analysis. Results were analyzed using SAS/STAT software package, SAS Institute Inc., USA (34). Statistical significance level was set to P<0.05.

Results

Distribution of 72Arg/Pro polymorphic variants. TP53 codon 72 polymorphisms in different PTC groups and controls were examined by two independent methods, real-time PCR allelic discrimination assay and direct sequencing (Fig. 1). The two methods were always concordant. None of the groups deviated from Hardy-Weinberger equilibrium with the allele frequencies of 0.72 and 0.28 (Arg and Pro, respectively) in the population or significantly differed from each other by \( \chi^2 \) test. At the same time, analysis demonstrated that there was a significantly lower number of homozygous Arg cases in the adult radiation-associated group compared to general population and sporadic PTCs whereas none of the other groups displayed such a feature (Table II). In the younger patients with radiation-related PTC, the frequency of the homozygous Arg genotype was somewhat lower than in sporadic PTCs and controls but this difference was insignificant. Neither sporadic PTC group vs. controls nor the two radiation-associated PTC groups displayed a significant difference for either genotype upon comparison.

The prevalence of heterozygous Arg/Pro genotype was elevated in the adult radiation-associated PTC group. Statistical analysis detected a significant difference between Arg/Pro rate in this group compared to sporadic PTCs. Comparison to population control also detected the increased prevalence of Arg/Pro cases in the adult radiation-associated group but threshold of significance was not reached. None of the other groups was found to be significantly different for this genotype in any combination.

Homoyzgous Pro genotype was relatively rare in any of the groups examined and resulted in insignificant difference between the radiation-associated cases and other groups. Also, no statistical difference was found between sporadic PTCs and controls.

Taken together, results demonstrate that the radiation-associated PTC group is characterized by an underrepresentation of the homozygous 72Arg-encoding genotype due to its significantly lowered prevalence in adult cases. This decrease may be largely attributed to the shift from homozygous Arg/Arg to heterozygous Arg/Pro genotype in this group.

In addition, we analyzed allele frequency association with individuals' gender and age. No correlation with gender (P=0.73) or age dependence (P=0.41 for trend) was detected using population control as a group for calculations.

Loss of heterozygosity of TP53 in PTCs. To detect possible allelic loss in the tumor, DNA specimens from corresponding normal thyroid tissue of the cases determined to be homozygous for either of genotypes in the tumor were subjected to allelic discrimination assay. Comparison of the TP53 status in the tumor and normal thyroid tissue showed perfect match between the two types of DNA from the same individual (data not shown) consistent with known infrequent alterations of the TP53 locus in differentiated thyroid cancers.

Expression levels of TP53 72Arg and 72Pro-encoding alleles in tumor and normal thyroid tissues. The proportion of individuals heterozygous for the TP53 72Arg/Pro polymorphism was relatively high in both radiation-associated and sporadic PTC groups. To evaluate the expression levels of each of the TP53 alleles in the tumor and normal thyroid tissue in such individuals, DNA-free RNA was purified, reverse transcribed and analyzed by real-time PCR. Relative expression...
levels of either allele were found to be balanced, being nearly equivalent in tumor tissue and normal counterpart in vast majority of cases (34 of 37 heterozygous cases examined, 91.9%) in both radiation-associated and sporadic PTC groups (Fig. 2). Only 3 paired specimens, for unknown reasons, showed an imbalanced, Arg>Pro or Arg<Pro, profile which was present in both tumor and normal tissue (representatively shown in Fig. 2).

Correlation of TP53 polymorphism with tumor clinicopathological characteristics. Approximately a half of childhood/adolescent PTCs (23/47, 48.9%) and a slightly smaller
finding is further strengthened by the lack of adult patients compared to the sporadic PTC group. This of its association with younger age of the radiation-exposed was revealed compared to the sporadic PTCs and control cases, therefore older age of patients in the adult group was radiation-associated childhood/adolescent and adult PTC population. Latency was found to be nearly even in the association with individuals’ age and gender in the control genotype deficiency was not observed ruling out the possibility of of PTCs and sporadic cases. A significantly decreased number different age or etiology.

Assessment of TP53 variant correlation with other clinicopathological parameters showed no link to tumor stage and indices of tumor aggressiveness such as local lymph node involvement and presence of distant metastases. The only exception was a significant overrepresentation of cases with positive locoregional lymph nodes in the radiation-associated pediatric/adolescent PTC group homozygous for 72Arg-encoding allele (P=0.02). In heterozygous Arg/Pro individuals from the same group there was a tendency to lower incidence of lymph node involvement compared to patients with other TP53 genotypes. On the contrary, in the radiation-associated adult PTCs, TP53 heterozygosity strongly tended to associate with increased rate of metastases to local lymph nodes. However, for both of these, the trends was statistically insignificant (P=0.08 and P=0.05, respectively). In the sporadic PTC group, no genotype-phenotype associations were observed.

Altogether, the data demonstrate that none of TP53 genotypes is likely to be specifically linked to histological tumor variants in PTC. Some particular associations may occur within certain age groups with regard to the local lymph node status but these are not necessarily paralleled in other PTC groups of different age or etiology.

Discussion

In this study, we have analyzed TP53 72Arg- or 72Pro-encoding allele distribution in two radiation-associated groups of PTCs and sporadic cases. A significantly decreased number of Arg/Arg patients in the adult radiation-associated PTC group was revealed compared to the sporadic PTCs and control population. In pediatric/adolescent PTCs, homozygous Arg genotype deficiency was not observed ruling out the possibility of its association with younger age of the radiation-exposed adult patients compared to the sporadic PTC group. This finding is further strengthened by the lack of TP53 genotype association with individuals’ age and gender in the control population. Latency was found to be nearly even in the radiation-associated childhood/adolescent and adult PTC cases, therefore older age of patients in the adult group was due to the older age at presumed exposure but not to the longer period of time between exposure and disease onset. Hence, underrepresentation of homozygous Arg is specific to adult post-Chernobyl patients which may suggest an age related difference in the thyroid’s biological reaction to radiation exposure. It is tempting to speculate that such a difference may in part be dependent on the propensity of the 72Pro p53 isofrom to induce cell death less efficiently, but age-associated particularities of this biological framework remain to be clarified.

Next, we addressed a question whether TP53 loss of heterozygosity, a mechanism of tumor suppressor gene inactivation in various types of human cancers, might have taken place in the studied PTCs. Our results are in agreement with previous reports of infrequent allelic loss and/or TP53 gene mutation in PTC which are more common in undifferentiated thyroid cancer (29,35,36). In addition, we determined that expression levels of Arg- and Pro-encoding alleles in heterozygous cases were essentially even in both PTC tissue and normal thyroid counterpart suggesting no cancer-associated bias or imprinting. It has been shown that imbalanced allele expression of a tumor suppressor gene may be linked to cancer risk (37). Our data demonstrate this has not been the case for radiation-associated or sporadic PTCs, at least with respect to TP53. In approximately 10% of patients biased allele expression was detected, but interestingly, this was present in both the tumor and normal thyroid tissues from the same individual. Therefore, it was not a result of cell transformation, but rather a systemic (epi)genetic modification whose nature in each particular case may be different and comprise a matter of a separate investigation.

We also attempted to verify TP53 genotype association with PTC morphology. Histological features of post-Chernobyl PTCs have been shown to markedly differ from those of sporadic adult PTCs (38,39), a circumstance that may potentially be misleading if genotype-morphology comparison was performed between PTC groups of different ages at operation. When analysis was done within each separate PTC group, no significant association was revealed between particular TP53 genotype and major histological component of the tumor. There has been no data in the literature on TP53 polymorphism association with thyroid cancer morphology to compare, but results obtained for other types of human malignancies, such as ovarian (40) and gastric cancer (41), suggest such correlation may not be commonly linked to a germline polymorphism.

No association has been previously found between PTC aggressiveness and p53 polymorphism (15). Our results support this in respect of sporadic PTC cases. However, in the post-Chernobyl cases, a significant correlation with lymph node involvement occurred in radiation-associated pediatric/adolescent subgroup homozygous for Arg allele whereas the Arg/Pro genotype displayed a tendency to an inverse association. In radiation-associated adult PTCs, we were unable to demonstrate the same correlation. This, apparently age-dependent difference, may be explained, at least in part, by the differing TP53 genotype prevalence in radiation-associated pediatric/adolescent and adult subgroups. Homozygous Arg and heterozygous Arg/Pro accounted for about 90% of cases in these subgroups; lymph node involvement was present in
half of the adult radiation-associated cases and in slightly greater proportion of pediatric/adolescent PTCs. Since relative numerical superiority of homozygous Arg cases in the younger subgroup is higher than in adults, it becomes possible to trace the mentioned finding. It is also possible that the association between TP53 genotype and lymph node involvement may interact with the age-related molecular biological profile of PTC. Rearrangements, such as ret/PTC (42,43) or the recently discovered AKAP9-BRAF fusion (44) are more common in PTC patients diagnosed at a younger age, whereas BRAFV600E transversion occurs mostly in adult PTCs (45-47). At present, nothing has been reported on the cross-talk between thyroid-specific activated oncogenic proteins and p53 isoforms, or on the impact of such cooperation on the biological behavior of a tumor.

Our data are at some variance with Granja et al findings who have shown a significant overrepresentation of homozygous Pro genotype in Brazilian PTC patients with respect to a control population (15). The main factor accounting for such a discrepancy may be a difference in the genetic background of individuals enrolled in the reported and present studies: our estimates show a significant difference between the genotype distribution in Brazilian and Russian-Ukrainian population (P<0.0001, χ2 test), resulting in a lower proportion of homozygous Pro individuals in the former. On the other hand, allelic frequencies in our control group were similar to those previously reported in healthy individuals from USA (Caucasian women) (48), England (19), Germany (20) and Czech (21). In a study of German patients with thyroid cancer, Boltze et al found PTC to be devoid of homozygous Pro genotype (14), but this was challenged by the Brazilian laboratory (15). In our series, we also detected Pro/Pro in PTCs at nearly the same frequency as it was in the group(s) of comparison, perhaps due to greater number of cases examined by us than in the cited work (n=21). Thus, our results indicate that homozygous Pro genotype may occur in Caucasians with PTC, and that TP53 allelic prevalence may vary in PTC patients with differing genetic backgrounds.

In summary, our data show, for the first time, a significant decrease of homozygous Arg TP53 genotype prevalence in adult patients with radiation-associated PTC as compared to sporadic PTC cases and general population suggestive that other TP53 allele combinations may contribute to a risk of papillary thyroid cancer in individuals exposed during their late childhood, adolescence or in young adult age (for females). In the tumors, cell transformation does not lead to allelic loss or biased TP53 allele expression in heterozygous individuals. None of TP53 genotypes specifically associates with tumor morphology, however, some particular correlations with manifestations of tumor aggressiveness may occur in certain age groups of radiation-associated but not in adult sporadic PTCs. We assume these data together with elucidation of other individual genetic characteristics, which is an intriguing future experimental task, may be of importance for identification of groups at risk for radiation-associated thyroid cancer both retrospectively and prospectively if exposure is anticipated. Also, our results indicate that TP53 polymorphic status needs to be taken into account for correct planning and interpretation of studies on radiation health effects on the human thyroid.

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