Childhood Thyroid Cancer: Comparison of Japan and Belarus

Yutaka SHIRAHIGE, Masahiro ITO*, Kiyoto ASHIZAWA, Tomoko MOTOMURA, Naokata YOKOYAMA, Hiroyuki NAMBA**, Shuji FUKATA***, Tamotsu YOKOZAWA***, Naofumi ISHIKAWA\#, Takashi MIMURA\#, Shunichi YAMASHITA**, Ichiro SEKINE*, Kanji KUMA***, Kunihiko ITO\#, and Shigenobu NAGATAKI

First Department of Internal Medicine, Departments of *Molecular Pathology and
**Nature Medicine, Atomic Bomb Disease Institute, Nagasaki University School of Medicine, Nagasaki 852-8501,
***Kuma Hospital, Kobe 650-0011, and \#Ito Hospital, Tokyo 150-0001, Japan

Abstract. The high incidence of childhood thyroid cancer in Belarus is suspected to be due to radiation exposure after the Chernobyl reactor accident. To clarify the clinical and histological characteristics of childhood thyroid cancer in Belarus, we therefore compared these patients to a radiation non-exposed control series in Japan. In Belarus, 26 thyroid cancers in subjects aged 15 or younger were diagnosed among 25,000 screened between 1991 and 1995 by Chernobyl-Sasakawa Health and Medical Cooperation Project. The clinical and morphologic features of these 26 cases were compared to 37 childhood thyroid cancers in Japan diagnosed between 1962 and 1995. The age distribution at operation in Belarus showed a peak at 10 years old, with a subsequent fall in numbers. In contrast, the age distribution at operation in Japan showed a smooth increase between the ages of 8 and 14. The mean tumor diameter was smaller in Belarus than that in Japan (1.4 ± 0.7 *vs.* 4.1 ± 1.7 cm, $P<0.001$). The sex ratio, regional lymph node metastasis, extension to surrounding tissues or lung metastasis did not differ significantly. Histologically, all cases in Belarus were papillary and in Japan 33 cases were papillary and 4 cases were follicular carcinomas. Among papillary carcinomas, the frequency of a solid growth pattern, a criteria for classifying a tumor as poorly differentiated, was higher in Belarus than that in Japan (61.5 *vs.* 18.2%, $P<0.001$). The difference between the features of childhood thyroid cancer in Japan and Belarus may be due to the difference in the process of carcinogenesis, but more direct evidence and further analysis by molecular epidemiology are needed in Belarussian cases.

Key words: Chernobyl, Japan, Radiation, Thyroid neoplasms, Children

(*Endocrine Journal* 45: 203–209, 1998)

THE Chernobyl Nuclear Plant accident on April 26, 1986, has resulted in a wide range of both actual and potential health problems. The incidence of childhood thyroid cancer had risen sharply in the Republic of Belarus, especially around the Gomel region only 4 years after the accident [1, 2]. A similar yearly increase tendency is observed also in Ukraine and Russia [3]. The number of cases that had occurred between 1986 and 1995 in Belarus, a country with a population of 10.3 million, was reported to be 424 [3]. In the Ukraine, with a population of 60 million, 211 cases occurred between 1986 and 1994 [3]. In the Russian Federation, only one child with thyroid cancer was recorded between 1986 and 1989, but between 1990 and 1994, 23 cases of thyroid carcinoma were reported in children [3]. Although these patients

are concentrated in highly contaminated areas, especially in the Gomel region in the Republic of Belarus, doses of exposure have not been accurately determined. The association between radiation exposure and development of thyroid carcinoma is well documented [4]. The incidence of childhood thyroid cancer is extremely rare and the baseline incidence of naturally occuring thyroid carcinoma is variable [5]. Furthermore, the mechanism of radiation-associated carcinogenesis of the thyroid gland is poorly understood, although the thyroid gland is highly sensitive to external radiation exposure [4]. All of the preceding thyroid carcinomas developed after longer latency periods, whereas tumors arising in the Chernobyl population began developing with surprising rapidity and short latency. The investigation of childhood thyroid cancer is, therefore, needed to clarify the difference between the characteristics of the radiation exposed and non-exposed groups. The histopathological findings of childhood thyroid cancer after the Chernobyl accident have been reported [6, 7] and comparative analysis of epidemiological, clinical and morphological features of malignant and benign thyroid lesions from patients exposed to radiation in Belarus as a result of the Chernobyl accident has also been described [8].

In this report, a comparison of these cases with a radiation non-exposed control series obtained from Japanese cases was made, in which significant and important information might be obtained.

Materials and Methods

Ultrasonographic screening of childhood thyroid diseases started at Gomel Specialized Medical Dispensary in May, 1991 as a part of the Chernobyl-Sasakawa Health and Medical Cooperation Project [9]. Health screening services were provided for children aged 0–10 years old at the time of the accident. 25,000 children were screened only once between May, 1991 and June, 1995, and children suspected of having thyroid cancer as a result of ultrasonography or fine-needle aspiration biopsy were referred to the Belarus Thyroid Tumor Center in Minsk for further examination. Up to June, 1995, 29 thyroid cancer cases were diagnosed and operated on. 26 patients aged 15 years or younger

at operation were analyzed as childhood thyroid cancers in this study.

In Japan, between 1962 and 1995, 27 cases and 10 cases, respectively, were diagnosed and treated at Ito Hospital, Tokyo and Kuma Hospital, Kobe. These patients in Japan had no prior history of internal or external irradiation. The mean follow-up period after the initial visit was 129.4 ± 82.1 months. They were 15 years old or younger at the time of the initial treatment. Pathohistological examination included establishment and re-confirmation of the diagnosis, classification according to the World Health Organization classification (2nd eds) [10], staging according to the TNM system of the UICC [11].

Statistics

The Student t test with double-sided confidence limits, the chi-square method or Fisher's exact probability test were used. Two values were considered significantly different when the probability of P was less than 0.05.

Results

Age and sex

In Belarus, there were 18 girls and 8 boys ranging in age from 5 to 15 years with a mean age of 10.6 years at operation (Table 1). This was significantly younger than that of the Japanese patients (11.9 years old, $P=0.03$). As shown in Fig. 1, the age distribution at operation in a study of 37 children with thyroid cancer in Japan showed a smooth increase between the ages of 8 and 14. In contrast, the age distribution at operation in Belarus showed a peak at 10 years old, with a subsequent decrease in the number. Analysis of Belarussian cases showed that the age at operation become older with the year of operation (Fig. 2). This observation is consistent with a cohort effect, with one age group of children carrying an increased risk of developing thyroid cancer. The age at the time of the accident in Belarus ranged from 0.2–7.4 years with a mean age of 2.7 years. The age distribution of these cases is shown in Fig. 3. The highest number of patients that subsequently developed thyroid carcinomas were in the group that were less than 1 year of age

Table 1.   Childhood thyroid cancer in Japan and Belarus

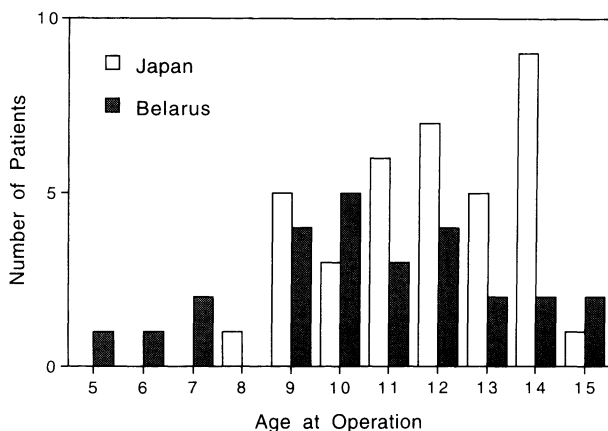|	Japan (37 cases)	Belarus (26 cases)	P values
Age at operation	11.9 ± 1.9	10.6 ± 2.6	0.03
Female/Male ratio	4.3:1	2.3:1	N.S.
Mean tumor size (cm)	4.1 ± 1.7	1.4 ± 0.7	< 0.001
Regional lymph node metastasis	27 (73%)	19 (73%)	N.S.
Extension to surrounding tissues	13 (35%)	14 (54%)	N.S. (P=0.14)
Pulmonary metastasis	7 (19%)	1 (4%)	N.S. (P=0.08)
Histological type			
Papillary carcinoma	33 (89%)	26 (100%)	
Follicular carcinoma	4 (11%)	0 (0%)	N.S. (P=0.11)
Histological subtype of papillary carcinoma			
Solid component			
20% <	6 (18.2%)	16 (61.5%)	< 0.001
60% <	4 (12.1%)	9 (34.6%)	0.04
Follicular component			
20% <	11 (33.3%)	10 (38.5%)	N.S.
60% <	5 (15.2%)	5 (19.2%)	N.S.
Follicular variant	0 (0%)	2 (7.7%)	N.S. (P=0.19)
Papillary component			
90% <	17 (51.5%)	3 (11.5%)	0.001

Fig. 1.   Age distributions of patients with thyroid cancer in Japan and Belarus at the time of the initial operation.
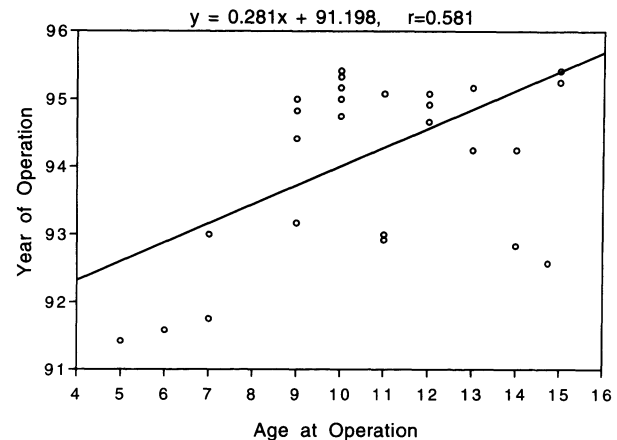

Fig. 2.   Relationship between the year of operation and age at operation in Belarus.

at the time of the accident.

The overall female-to-male ratio among the Belarussian children was 2.3:1. This proportion was lower than that found in the series of Japanese children, though it was not statistically significant. This low female-to-male ratio is in accordance with the earlier report of post-Chernobyl thyroid cancer in Belarus [6].

In the current study, the period of time between the nuclear accident and the surgical treatment

ranged from 4.5 years to 9.2 years, with an average of 7.9 years.

Histopathological findings

As shown in Table 1, histologically, all cases in Belarus were classified as papillary and in Japan 33 cases were papillary and 4 cases were follicular carcinomas. Among papillary carcinomas, typical (classic) papillary carcinomas were found more
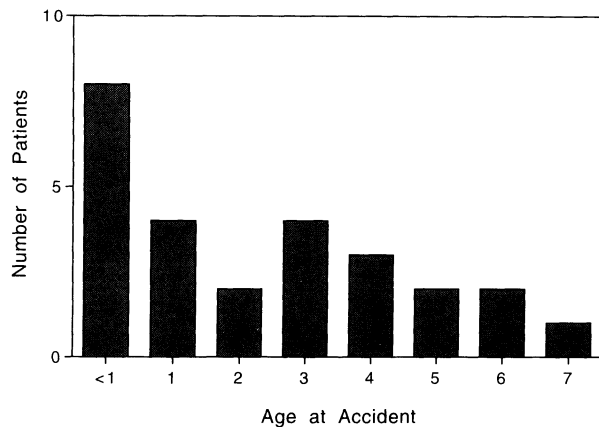
Fig. 3.   Age distributions of patients with thyroid cancer in Belarus at the time of the Chernobyl accident.

Fig. 4.   Histological findings of papillary carcinoma obtained in Japan (H & E, original magnification × 50).

frequently in the cases in Japan (51.5 vs. 11.5%, P=0.001, Fig. 4). The incidence of a solid growth pattern occupying more than 20% of the whole tumor was unexpectedly higher in Belarus than in Japan (61.5 vs. 18.2%, P<0.001, Fig. 5). Among Japanese cases, the incidence of a solid growth pattern was independent of the tumor size. The presence of a solid area can be considered as a sufficient criterion for classifying a tumor as poorly differentiated. Psammoma bodies, consisting of calcific bodies with concentric lamination, and thick stromal fibrosis were observed more frequently in the cases in Belarus (Fig. 6). Atypical fibroblast and vascular hyperplasia, which are known as late irradiation effects, were not observed in our Belarussian series.

Fig. 5.   Solid component of papillary carcinoma in Belarus. Nuclear characteristics were confirmed in the solid proliferative nests (H & E, original magnification × 66).

Tumor stage

The differences in tumor stage are shown in Fig. 7. Although large intrathyroidal tumors were infrequent in Belarus, invasion of extrathyroidal tissues was observed in 14 cases (54%), often in carcinomas of restricted size, i. e. mean diameter 1.6 cm. Small intrathyroidal tumors (T1) were more frequent in the cases in Belarus, indicating a smaller mean tumor diameter in Belarus than in Japan (1.4 ± 0.7 vs. 4.1 ± 1.7 cm, P<0.001). Regional lymph node metastases, soft tissue invasion and pulmonary metastasis at operation were not significantly different from the findings in Japanese children.
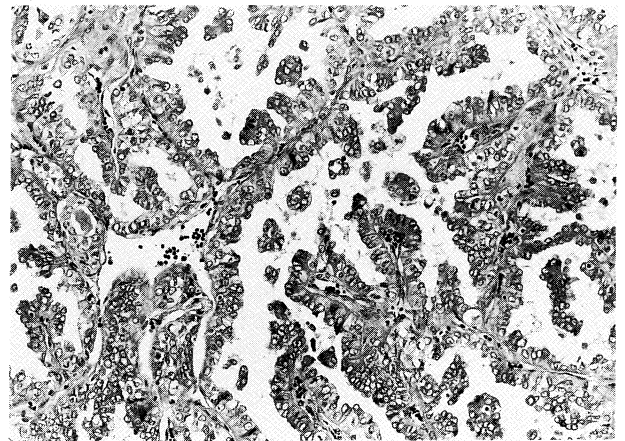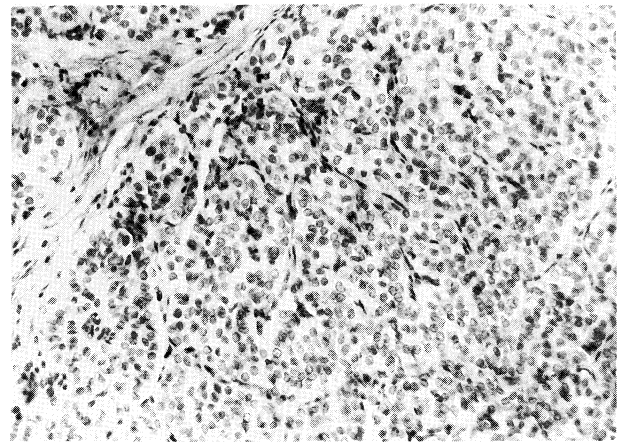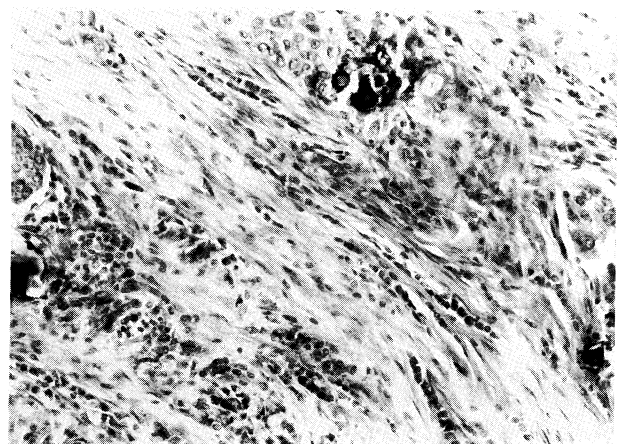

Fig. 6.   Marked fibrosis with foci of calcification observed in this Belarussian case. (H & E, original magnification × 66).
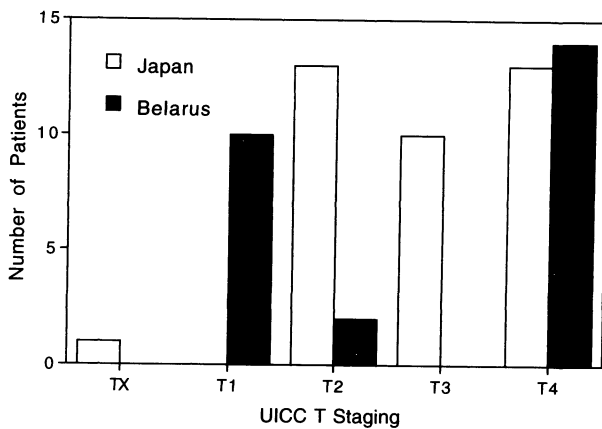
Fig. 7.   Comparison of UICC T-stages in Japan and Belarus.

Follow-up study

Although no follow-up results are yet available for the children in Belarus, we could observe Japanese patients for a long period. We presented these follow-up data because they provide us with useful information on how the children should be treated and cared for after the Chernobyl accident. The follow up period for 37 Japanese patients with primary tumor ranged from 10 months to 23.6 years, with a mean of 129.4 months. All 7 patients who had lung metastasis at initial surgery were subsequently treated with ^{131}I 3–8 times (180–689 mCi). These patients are all alive.

After the initial operation, cervical lymph node metastases were seen in 4 patients and lung metastases were observed in 3 patients. Patients with cervical lymph node metastases underwent additional neck dissections of newly developed lesions. The patients with lung metastasis were treated with ^{131}I. These patients with disease recurrence were treated adequately and all are still alive.

Among 37 cases in Japan, one patient with papillary carcinoma died 11 years after the surgical treatment. The patient was 14-year-old female at the time of operation and negative for distant metastasis at the initial treatment. The tumor was multifocal and extended to surrounding tissues ($T_{4b}N_1M_0$). Total thyroidectomy was performed, but radical neck dissection was impossible because of the marked adhesion of regional lymph node metastases to surrounding tissues.

Discussion

The evidence presented in this report shows clearly that there is a major difference between thyroid cancers in children in Japan and Belarus, although radiation exposure, hereditary and/or circumstantial factors need to be considered when interpreting these results. In addition, the characteristics of a large number of childhood thyroid cancers in Japan are presented for the first time.

The largest number of patients that subsequently developed thyroid carcinomas in this report were in the group less than 1 year of age at the time of the Chernobyl accident. One of the possible explanations of the importance of age at exposure might be related to the difference between the radiation doses in younger and older children. High sensitivity to the carcinogenic effect of radiation in young children has already been reported [4], the relative risk being 3 times higher for children aged less than 5 years at exposure than for those aged 10–19 among atomic bomb survivors [12]. The doses absorbed after the Chernobyl accident are reported to be 3–10 times higher in children than in adults and greater in younger children than in older ones [13, 14].

The short interval between radiation exposure and the time of histologic diagnosis has been reported to be a characteristic feature of post-Chernobyl thyroid cancers. On the other hand, thyroid cancer appeared in substantial numbers in the 10 years or more after exposure among Japanese atomic bomb survivors [15–17]. In Marshallese, exposed to a mixture of radioiodines and gamma radiation, thyroid malignancies were detected 10–21 years after the nuclear explosion [18]. Various studies of childhood thyroid cancers after exposure of the head and neck to external irradiation demonstrate a latent interval of 3.5–18 years, with the average time between X-ray therapy and tumor development varying from 6.3 to 9.6 years [19–23]. The National Council of Radiation Protection and Measurement recommends using a minimum induction period of 5 years in the calculation of risk of radiation-induced thyroid cancer [24]. Furmanchuk reports a mean latent interval of 4.4 years with the entire series of tumors diagnosed between 1986 and 1991 [6]. In the patho-

morphologic study of 84 cases in the Republic of Belarus diagnosed between 1991 and 1992, the mean latency period is 5.8 years [7]. In the current study, when analyzing cases up to 1995, the period of time between the nuclear accident and the surgical treatment was 7.9 years. Since latency period of post Chernobyl thyroid cancer is becoming longer, further observation is needed in order to draw a conclusion.

The mean tumor diameter was smaller in Belarus than that in Japan (1.4 ± 0.7 *vs.* 4.1 ± 1.7 cm, $P<0.001$). The difference of the tumor size might be related to the intensive surveillance of the disease around Chernobyl.

The histological findings of childhood thyroid cancer in Belarus in this report are similar to those reported previously [6, 7]. Papillary carcinoma is a predominant type of pediatric thyroid cancer around Chernobyl [6, 7]. A high incidence of poorly differentiated components (solid components), thick stromal fibrosis and psammoma bodies are also common findings. The incidence of a solid growth pattern in Belarussian cases was unexpectedly higher than in the radiation non-exposed series in Japan. This indicates the aggressive potential of thyroid cancers in Belarus, since the presence of a solid area can be considered to be a sufficient criterion for classifying a tumor as poorly differentiated [6, 25]. In fact, a high percentage of the carcinomas in Belarus showed extrathyroidal spread despite their restricted size, but only short term follow-up data after the initial surgery in Belarus are yet available. In this study, we could observe 37 Japanese cases, with a mean follow-up period of 129.4 months. Only one patient died 11

years after the initial non-curative operation. 7 had disease recurrence and they have all been kept alive by adequate adjuvant therapy. The clinical and histological characteristics of the Japanese cases overlap those seen in Western countries [26–29]. Complete and continuing follow-up after the initial treatment is indeed necessary, especially for the cases in Belarus, to establish optimal therapy.

Although we have not yet evaluated the gene abnormalities in these thyroid cancer tissues, a high prevalence of *RET* rearrangement and mutations in the p53 tumor suppressor gene in thyroid tumors of children from Belarus after the Chernobyl accident have been reported [30, 31]. Molecular biology will be one of the major strategies for detecting radiation-specific gene abnormalities in the future.

In conclusion, the histological differences between childhood thyroid cancer in Japan and Belarus might be reflected in a different process of carcinogenesis, such as radiation exposure, hereditary and/or circumstantial factors. Since the childhood thyroid cancers in Belarus appears to be more aggressive than the radiation non-exposed series in Japan, intensive care and long-term follow-up after the initial treatment are essential.

Acknowledgements

References

1. Kazakov VS, Demidchik EP, Astakhova LN (1992) Thyroid cancer after Chernobyl. *Nature* 359: 21.
2. Baverstock K, Egloff B, Pinchera A, Ruchti C, Williams D (1992) Thyroid cancer after Chernobyl. *Nature* 359: 21–22.
3. Williams ED (1996) Effects on the thyroid in populations exposed to radiation as a result of the Chernobyl accident. In: Delves D, Demir M (eds) One Decade after Chernobyl: Summing Up the Consequences of the Accident. International Atomic Energy Agency, Vienna, 207–230.
4. Ron E, Lubin JH, Shore RE, Mabuchi K, Modan B,

Pottern LM, Schneider AB, Tucker MA, Boice JD Jr (1995) Thyroid cancer after exposure to external radiation: A pooled analysis of seven studies. *Radiat Res* 141: 259–277.
5. Segal RL (1992) Radiation-induced thyroid carcinoma. In: Cobin RH, Sirota DK (eds) Malignant Tumors of the Thyroid: Clinical Concepts and Controversies. Springer-Verlag New York Inc., New York, 32–44.
6. Furmanchuk AW, Averkin JI, Egloff B, Ruchti C, Abelin T, Schappi W, Korotkevich EA (1992) Pathomorphological findings in thyroid cancers of

children from the Republic of Belarus: A study of 86 cases occurring between 1986 ('post-Chernobyl') and 1991. *Histopathology* 21: 401–408.

7. Nikiforov Y, Gnepp DR (1994) Pediatric thyroid cancer after the Chernobyl disaster. *Cancer* 74: 748–766.

8. Nikiforov Y, Gnepp DR, Fagin JA (1996) Thyroid lesions in children and adolescents after the Chernobyl disaster: Implications for the study of radiation tumorigenesis. *J Clin Endocrinol Metab* 81: 9–14.

9. Derzhitskii VE, Panasyuk GD, Derzhitskaya NK, Demidenko AN, Kalimulin VA, Anikina IV, Cot VA, Masyakin VB (1996) Results of the examination of the health status of children in Gomel oblast 1991–1994 Chernobyl Sasakawa Project. In: Yamashita S, Fujimura K, Hoshi M, Shibata Y (eds) A Report on the 1994 Chernobyl Sasakawa Project Workshop. Sasakawa Memorial Health Foundation, Tokyo, 27–53.

10. Hedinger Chr, Williams ED, Sobin LH (1988) Histological Typing of Thyroid Tumours. 2nd rev. ed. (International histological classification of tumours; 11) Springer-Verlag, Berlin.

11. Hermanek P, Sobin LH (eds) (1987) TNM Classification of Malignant Tumors. 4th rev. ed. Springer-Verlag, Berlin 36–38.

12. Akiba S, Lubin J, Ezaki H, Ron E, Ishimaru T, Asano M, Shimizu Y, Kato H (1 991) Thyroid cancer incidence among atomic bomb survivors, 1958–79. Radiation Effect Research Foundation. TR5–91.

13. Castronovo FP Jr (1987) Iodine-131 thyroid uptake results in travelers returning from Europe after the Chernobyl accident. *J Nucl Med* 28: 535–541.

14. Malone J, Unger J, Delange F, Lagasse R, Dumont JE (1991) Thyroid consequences of Chernobyl accident in the countries of the European community. *J Endocrinol Invest* 14: 701–717.

15. Parker LN, Belsky JL, Yamamoto T, Kawamoto S, Keehn RJ (1974) Thyroid carcinoma after exposure to atomic radiation: A continuing survey of a fixed population, Hiroshima and Nagasaki, 1958–1971. *Ann Intern Med* 80: 600–604.

16. Takeichi N, Ezaki H, Dohi K (1991) Thyroid cancer: Reports up to date and a review. *J Radiat Res* Suppl: 180–188.

17. Socolow EL, Hashizume A, Neriishi S, Niitani R (1963) Thyroid carcinoma in man after exposure to ionizing radiation. *N Engl J Med* 268: 406–410.

18. Conard RA (1984) Late radiation effects in Marshall islanders exposed to fallout 28 years ago. In: Boice JD, Fraumeni JF (eds) Radiation Carcinogenesis: Epidemiology and Biological Significance. Raven Press, New York, 57–71.

19. Winship T, Rosvoll RV (1970) Thyroid carcinoma in childhood: Final report on a 20 year study. *Clin Proc Children's Hosp* 26: 327–348.

20. Harness JK, Thompson NW, Nishiyama RH (1971) Childhood thyroid carcinoma. *Arch Surg* 102: 278–284.

21. Liechty RD, Safaie-Shirazi S, Soper RT (1972) Carcinoma of the thyroid in children. *Surg Gynecol Obstet* 134: 595–599.

22. Doci R, Pilotti S, Costa A, Semerado G, Cascinelli N (1978) Thyroid cancer in childhood. *Tumori* 64: 649–657.

23. Segal K, Levy R, Sidi J, Abraham A (1985) Thyroid carcinoma in children and adolescents. *Ann Otol Rhinol Laryngol* 94: 346–349.

24. National Council on Radiation Protection and Measurements (NCRP) (1985) Induction of thyroid cancer by ionizing radiation. NCRP reports, Bethesda (MD), 80.

25. Tscholl-Ducommun J, Hedinger ChrE (1982) Papillary thyroid carcinomas: Morphology and prognosis. *Virchows Arch A Pathol Anat Histol* 396: 19–39.

26. Tallroth E, Backdahl M, Einhorn J, Lundell G, Lowhagen T, Silfversward C (1986) Thyroid carcinoma in children and adolescents. *Cancer* 58: 2329–2332.

27. Schlumberger M, De Vathaire F, Travagli JP, Vassal G, Lemerle J, Parmentier C, Tubiana M (1987) Differentiated thyroid carcinoma in childhood: Long term follow-up of 72 patients. *J Clin Endocrinol Metab* 65: 1088–1094.

28. La Quaglia MP, Corbally MT, Heller G, Exelby PR, Brennan MF (1988) Reccurence and morbidity in differentiated thyroid carcinoma in children. *Surgery* 104: 1149–1156.

29. Herach HR, Williams ED (1995) Childhood thyroid cancer in England and Wales. *British J Cancer* 72: 777–783.

30. Klugbauer S, Legenfelder E, Demidchik EP, Rabes HM (1995) High prevalence of RET rearrangement in thyroid tumors of children from Belarus after the Chernobyl reactor accident. *Oncogene* 11: 2459–2467.

31. Hillebrandt S, Streffer C, Reiners Chr, Demidchik E (1996) Mutations in the p53 tumour suppressor gene in thyroid tumours of children from areas contaminated by the Chernobyl accident. *Int J Radiat Biol* 69: 39–45.