МЕДИЦИНСКИЕ АСПЕКТЫ ЧЕРНОБЫЛЬСКОЙ КАТАСТРОФЫ

CHERNOBYL BEYOND 20 YEARS: WHAT IS RADIATION-INDUCED THYROID CANCER?

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Along with a summary of clinical data on Chernobyl thyroid cancer, presented will be the scope of current understanding of the molecular mechanisms of radiation-induced thyroid cancer in children and adolescents with a focus on the discussion of how to further assist the long-term follow-up of the operated patients with thyroid cancer and to outline the approaches to the identification of the groups at high risk of the disease. Special attention should be paid to a high risk group of individuals who had been exposed to radioactive iodines after the Chernobyl accident and whose age is from 20 to 30 year-old in 2006.

Key words: thyroid cancer, molecular-genetics mechanism.

ЧЕРНОБЫЛЬ 20 ЛЕТ СПУСТЯ: К ВОПРОСУ О РАКЕ ЩИТОВИДНОЙ ЖЕЛЕЗЫ, ОБУСЛОВЛЕННОМ РАДИАЦИОННЫМ ФАКТОРОМ

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Наряду с данными клинических исследований в области рака щитовидной железы вследствие аварии на ЧАЭС, в статье рассматривается концепция молекулярного механизма возникновения РЩЖ у взрослых и детей, обусловленного радиационным фактором. Акцент ставится на методах долгосрочного ведения больных, перенесших операцию по поводу РЩЖ, и выявлении группы риска. Особое внимание следует уделять лицам, подвергнутым воздействию радиоактивного йода и чей возраст в 2006 году составляет 20–30 лет.

Ключевые слова: рак щитовидной железы, молекулярно-генетические механизмы.

Within and beyond the 21st Century Center of Excellence (COE) program in Nagasaki University, we have been deeply involved in various international joint projects from Japan on «Radiation Effects on Human Health» and are mainly trying to clarify the cause-and-effect relationship between Chernobyl radiation fallout problems and the existing health conditions including human cancers. Based on our medical aid projects and joint academic achievements around these areas, we have summrized the late health effects of radiation and learnt specific lessons from Atomic Bombing to Chernobyl through various on-going programs at the WHO Headquarter in Geneva [1].

Thyroid cancer is the most common type of human solid tumors associated with external ionizing radiation exposure, especially if irradiation occurs in neonates, infants and children [2]. Since the Chernobyl accident, specific attention has been paid to an internal exposure of the thyroid gland and its close relationship with childhood thyroid cancer [3]. The appropriate prophylaxis of iodine administration just after the accident like in Poland [4] could contribute to mitigate the increase of childhood thyroid cancer and also decrease the risk of thyroid cancer occurrence. Iodine deficiency is another risk factor of radiation-induced thyroid cancer around Chernobyl [5].

Childhood thyroid cancers are originally quite uncommon and have a fairly good prognosis despite of the aggressive manifestations. Incidence of thyroid cancer in children dramatically increased around Chernobyl from 1990 until 2000, probably attributed to short-lived radioactive iodines. About 4000 childhood and adolescent cases of thyroid cancers have been diagnosed from 1990 to 2001 around Chernobyl with few than 10 deaths reported [6]. Papillary carcinoma is the most common malignant tumor of the thyroid in both adults and in those 18 years of age and younger. There have been several reports of an association between radioactive iodine exposure and childhood thyroid cancer prevalence but the interpretation of data still needs some straightforward refining [7–11]. Adult thyroid cancers include disease types that range from an indolent small-size solitary malignant nodule to the fulminant and lethal anaplastic carcinoma. Definitely, the differences do exist between adult and childhood papillary thyroid cancers. For example, childhood thyroid cancers display a higher incidence of regional lymph node metastasis, extension outside the thyroid capsule and lung metastasis. The initial comparative study of post-Chernobyl thyroid cancer in Belarus and naturally occurring thyroid cancer in the Europe clearly demonstrated that individuals 5 year-old or less at the time of accident accounted for the majority of thyroid cancer patients substantiating a necessity of careful monitoring of the subjects of younger age at radiation exposure [12]. The prognosis of operated childhood thyroid cancer in Belarus is quite favorable so far [13]. There is no clear evidence at a moment that the incidence of thyroid cancer has increased among those exposed as adults [14, 15], however the role of adult radiation exposure, either by radioactive iodines or externally, remains to be clarified. Integrative to other conclusions, the Chernobyl Sasakawa Medical Aid Project performed from 1991 to 2001 has pointed out the necessity of a cooperative multidisciplinary thyroid cancer research system of the long-term health care of exposed individuals [16, 17].

Along with a summary of clinical data on Chernobyl thyroid cancer, presented will be the scope of current understanding of the molecular mechanisms of radiation-induced thyroid cancer in children and adolescents with a focus on the discussion of how to further assist the long-term follow-up of the operated patients with thyroid cancer and to outline the approaches to the identification of the groups at high risk of the disease.

1. Age distribution of thyroid cancer morbidity after the Chernobyl accident

The peak incidence of childhood thyroid cancer after the Chernobyl accident is now over, shifting from adolescents to young adult aged more than 20 year-old. The current latency between the Chernobyl accident and clinical diagnosis of thyroid cancer is also about 20 years. Time trends of thyroid cancer incidence are similar among the three affected countries, supporting the concept that subjects of younger age at the time of radiation exposure had, and continue to have, an elevated risk of developing thyroid cancers. The difference between early- and late-onset thyroid papillary thyroid cancers after the Chernobyl accident is under investigation but so far no clinical differences besides of age-related particularities have been registered between them.

2. How can we distinguish between radiation-induced and sporadic thyroid cancers?

High doses of ionizing radiation produce bulk damages in biological objects evoking one or another form of cell death. In contrast, low doses do not lead to apoptosis but induce numerous DNA double strand breaks, deletions, point mutations and/or chromosomal instability. There are three major approaches to the molecular discrimination between radiation-induced and sporadic thyroid cancers: 1) mutational studies in radiation-induced and sporadic thyroid tumors, 2) comparative gene expression studies, and 3) genomic studies including molecular epidemiology in patients who developed radiation-associated thyroid cancers. Resulting from cancer-related gene analysis, fusions between *RET* located on chromosome 10q11.2 and other genes are specifically found in papillary thyroid cancer tissues. These are collectively called *RET/PTC* rearrangements. Among 16 different types of *RET/PTC*s, *RET/PTC*1 and *RET/PTC*3 are the most common variants accounting for about 90% of all chimeric genes. The prevalence of *RET/PTC* rearrangements ranges from 11% to 43% in sporadic papillary thyroid cancers and 50–80% in patients with a history of radiation exposure. In children affected by the Chernobyl accident, *RET/PTC*3 was the most common type in tumors developed less than 10 years af-

ter the accident, whereas papillary thyroid cancers developed after the longer latency had predominantly *RET/PTC*1 (18). Another type of gene rearrangement, *AKAP9-BRAF* fusion, has been found in 11% of early onset papillary thyroid cancers but in 0% of tumors with the longer latency after the accident [19]. In contrast, point mutation analysis of RAS-RAF-MAPK cascade genes, such as *BRAF* and *RAS*, showed no significant difference of the mutational frequency between radiation-induced and sporadic thyroid cancers when similar age groups of patients were compared [20, 21].

As a whole, analysis of the mutational spectrum of the Chernobyl thyroid malignancies demonstrates that gene rearrangements leading to the activation of MAPK signaling appear to play a perceptible role in radiation-induced papillary thyroid cancer. However, none of the cancer genes or impaired tumor suppressor genes has proved a marker of radiation etiology. Moreover, gene expression patterns in radiation-related papillary thyroid cancers are similar to those in sporadic ones [22]. Therefore at a moment there is no established «radiation signature» or any specific target gene has been identified. Radiation-related gene abnormalities may actually be age-related.

3. Necessity of molecular epidemiology investigations

In view of the absence of genetic markers to distinguish between radiation-induced and sporadic papillary thyroid cancers, further genomic studies may give us critical hints of radiation sensitivity and tumor-prone susceptibility in man. Since our understanding is very limited as for why thyroid tumorigenesis occurs in a relatively small number of exposed individuals, large scale molecular epidemiology investigations in thoroughly designed cohorts around Chernobyl can potentially identify at the biochemical or molecular level specific exogenous and/or host factors which play a role in human cancer causation. Pilot studies suggest that molecular epidemiological methods targeting single nucleotide polymorphisms of DNA damage response and cell cycle control genes may be a promising tool in the area of radiation-induced carcinogenesis [23].

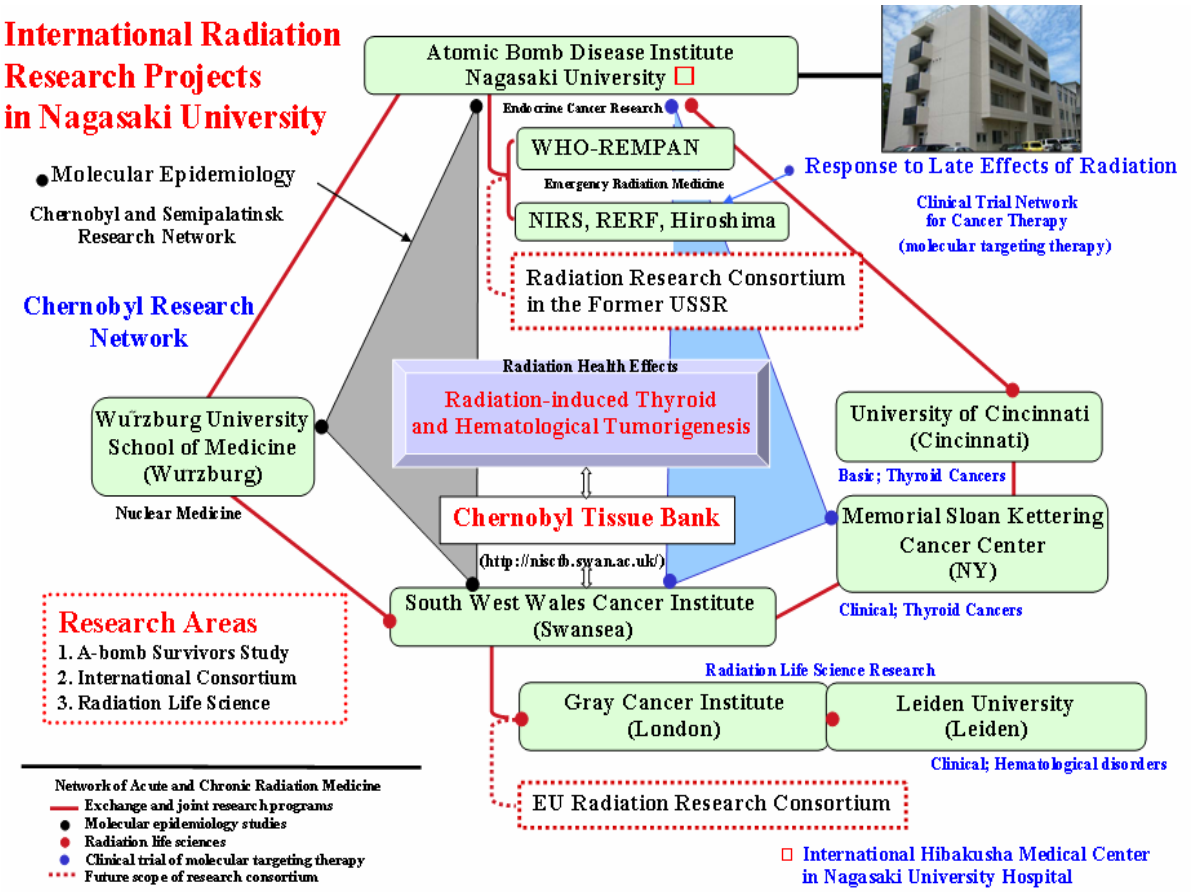
4. Hypothesis of radiation-induced thyroid carcinogenesis

Fundamental knowledge and hypothesis about radiation-induced leukemia mechanisms in children [24] may lead us to similar ideas in radiation-induced thyroid cancer. One can surmise that the risk of radiation-induce thyroid cancer in a population may be largely attributable to a small number of predisposed individuals in whom clonally expanded translocation-carrying pre-cancer cells have accumulated. The high frequency of *RET/PTC* rearrangement has been predominantly seen in the early onset cancers in young children after the Chernobyl accident; it seems to be declining gradually with patients' aging. The immature or precursor stem-cell like thyrocyte may be considered a preexisting initiated cell if it harbors *RET/PTC* rearrangement. Indeed, *RET/PTC* rearrangement alone is unlikely to be sufficient to transform human thyrocyte.

Thus, it is essentially needed to elucidate genetic particularities of patients with radiation-induced thyroid cancers. To test several possibilities of distinction between radiation-induced and sporadic thyroid papillary thyroid cancers, the ideal research bank of biological samples and data has been established as an international cooperative project, so called «Chernobyl Tissue Bank» [25].

5. Conclusion

Although radiation-induced thyroid cancer is a well-recognized medical phenomenon based on wide-ranged epidemiological studies, molecular signature(s) and other details of papillary thyroid cancer remain to be further clarified to pinpoint differential diagnostic criteria not only in childhood and adult thyroid cancers but also in radiation-induced and sporadic cancers. The latest study in Hiroshima and Nagasaki Atomic Bomb survivors in Japan has indicated that a biological effect from a single brief external exposure to ionizing radiation nearly 60 years in the past still occurs and can be detected [26]. Once during their childhood people are exposed even to low doses of ionizing radiation, either externally or internally, the cancer-prone cell damage within the thyroid gland can be preserved for a long time. Elucidation of the molecular mechanisms of radiation-induced thyroid cancer is, therefore, expected to contribute to the disease prevention and treatment in the coming future. Special attention should be paid to a high risk group of individuals who had been exposed to radioactive iodines after the Chernobyl accident and whose age is from 20 to 30 year-old in 2006.



REFERENCES

1. http://www.jstage.jst.go.jp/browse/amn/50/Supplement2/_contents.

2. *Ron E., Lubin J.H., Shore R.E. et al.* Thyroid cancer after exposure to external radiation; a pooled analysis of seven studies // Radiat Res. — 1995. — № 141. — P. 256–277.

3. *Kazakov V.S., Demidchik E.P., Astakhova L.N.* Thyroid cancer after Chernobyl // Nature. — 1992. — № 21. — P. 359.

4. *Nauman J., Wolff J.* Iodine prophylaxis in Poland after the Chernobyl reactor accident; benefits and risks // Am J Med. — 1993. — № 94. — P. 524–532.

5. *Ashizawa K., Shibata Y., Yamashita S. et al.* Prevalence of goiter and urinary iodine excretion levels in children around Chernobyl // J Clin Endocrinol Metab. — 1997. — № 82. — P. 3430–3433.

6. *Hatch M., Ron E., Bouville A., Zablotska Howe G.* The Chernobyl disaster: cancer following the accident at the Chernobyl Nuclear Power Plant // Epidemiol Rev. — 2005. — № 27. — P. 56–66.

7. *Likhtarev I.A., Sobolev B.G., Kairo I.A., Tronko N.D., Bogdanova T.I., Oleinic V.A., Epshtein E.V., Beral V.* Thyroid cancer in the Ukraine // Nature. — 1995. — № 375. — P. 365.

8. *Jacob P., Kenigsberg Y., Zvonova I. et al.* Childhood exposure due to the Chernobyl accident and thyroid cancer risk in contaminated areas of Belarus and Russia // Br J Cancer. — 1999. — № 80. — P. 1461–1469.

9. *Shibata Y., Yamashita S., Masyakin V.B., Panasyuk G.D., Nagataki S.* 15 years after Chernobyl: new evidence of thyroid cancer. — 2001. — № 358. — P. 1965–1966.

10. *Mahoney M.C., Lawvere S., Falkner K.L. et al.* Thyroid cancer incidence trends in Belarus: examining the impact of Chernobyl // Int J Epidemiology. — 2004. — № 33. — P. 1025–1033.

11. *Cardis E., Kesminiene A., Ivanov V. et al.* Risk of thyroid cancer after exposure of I-131 in childhood // J Natl Cancer Inst. — 2005. — № 97. — P. 727–732.

12. *Pacini F., Vorontsova T., Demidchik E.P. et al.* Post-Chernobyl thyroid carcinoma in Belarus children and adolescents: comparison with naturally occurring thyroid carcinoma in Italy and France // J Clin Endocrinol Metab. — 1997. — № 82. — P. 3563–3569.

13. *Demidchik Y.E., Demidchik E.P., Reiners C., Biko J., Mine M., Saenko V.A., Yamashita S.* Comprehensive clinical assessment of 740 cases of surgically treated thyroid cancer in children of Belarus // Ann Surg, in press. — April, 2006.

14. *Moysich K., Menezes R., Michalek A.* Chernobyl-related ionizing radiation exposure and cancer risk: an epidemiological review // Lancet Oncol. — 2002. — № 5. — P. 269–279.

15. *Ivanov V.K., Gorski A.I., Maksiutov M.A. et al.* Thyroid cancer incidence among adolescents and adults

in Bryansk redion of Russia following the Chernobyl accident // Health Phys. — 2003. — № 84. — P. 46–60.

16. *Yamashita S., Shibata Y.* Chernobyl // A Decade. Excerpta Medica, ICS 1156. — Amsterdam, 1997. — P. 613.

17. *Yamashita S., Shibata Y., Hoshi M., Fujimura K.* Chernobyl: Message for the 21st Century. Excerpta Medica ICS 1234. — Amsterdam, 2001. — P. 354.

18. *Rabes H., Demidchik E.P., Sidorov J.D., Lengfelder E., Beimfohr C., Hoelzel D., Klugbauer S.* Pattern of radiation-induced RET and NTRK1 rearrangements in 191 post-Chernobyl papillary thyroid carcinomas: biological, phenotypic and clinical implication // Clin Cancer Res. — 2000. — № 6. — P. 1093–1103.

19. *Ciampi R., Knauf J.A., Kerier R. et al.* Oncogenic AKFP0-BRAF fusion is a novel mechanism of MAPK pathway activation in thyroid cancer // J Clin Invest. — 2005. — № 115. — P. 94–101.

20. *Kumagai A., Namba H., Saenko V.A. et al.* Low frequency of BRAFT1796A mutations in childhood thyroid carcinomas // J Clin. Endocrinol. Metab. — 2004. — № 89. — P. 4280–4284.

21. *Lima J., Trovisco V., Soares P. et al.* BRAF mutations are not a major event in post-Chernobyl childhood thyroid carcinomas // J Clin. Endocrinol. Metab. — 2004. — № 89. — P. 4267–4271.

22. *Detours V., Wattel S., Venet D. et al.* Absence of a specific radiation signature in post-Chernobyl thyroid cancers // British J Cancer. — 2005. — № 92. — P. 1545–1552.

23. *Rogounovitch T.I., Saenko V.A., Ashizawa K., Sedliarou I.A., Namba H. et al.* TP53 codon 72 polymorphism in radiation-associated human papillary thyroid cancer // Oncol. Rep, in press. — 2006.

24. *Nakamura N.* A hypothesis: radiation-related leukaemia is mainly attributable to the small number of people who carry pre-existing clonally expanded preleukemic cells // Radiat Res. — 2005. — № 163. — P. 258–265.

25. http://www.chernobyltissuebank.com/.

26. *Imaizumi M., Usa T., Tominaga T. et al.* Radiation dose-response for thyroid nodules and autoimmune thyroid diseases in Hiroshima and Nagasaki Atomic Bomb Survivors 55–58 years after radiation exposure // JAMA. — 2006. — № 295. — P. 1011–1022.

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АНАЛИЗ РЕЗУЛЬТАТОВ РАДИАЦИОННЫХ ИССЛЕДОВАНИЙ, ПРОВЕДЕННЫХ ПОСЛЕ АВАРИИ НА ЧЕРНОБЫЛЬСКОЙ АЭС

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Рассматриваются результаты различного рода радиационных исследований, проведенных разными авторами после аварии на Чернобыльской АЭС. Проведен анализ полученных результатов на предмет их соответствия описанным в литературе процессам выноса радиоактивного вещества (РВ) из 4-го блока и его распространения в атмосфере. Рассмотрены реализованные радионуклидные соотношения в объектах окружающей среды. Следствием ядерной природы развития аварии на Чернобыльской АЭС является необходимость пересмотра вклада короткоживущих изотопов йода в дозу внутреннего облучения щитовидной железы, обусловленной поступлением в организм йода-131, для жителей территорий, расположенных в первичных направлениях распространения радиоактивного вещества.

Ключевые слова: авария, вынос радионуклидов, изотопные соотношения, йод-131, щитовидная железа.

DATA ANALYSIS OF RADIATION RESEARCH CONDUCTED AFTER CHERNOBYL DISASTER

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This article represents the results of various radiation research conducted by different authors after the Chernobyl disaster. The analysis of the results for their correspondence to the process of the radioactive substance release in the 4th block and its distribution in the air has been made. The article describes the realized radionuclide correlations between the environmental objects. The nuclear nature of the Chernobyl disaster resulted in the necessity to re-consider the contribu-